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                  substances identified in English-, French-, German-,
                  and Japanese-language basic patents from 2004-present
 NEWS  3  NOV 26  MARPAT enhanced with FSORT command
 NEWS  4  NOV 26  MEDLINE year-end processing temporarily halts
                  availability of new fully-indexed citations
 NEWS  5  NOV 26  CHEMSAFE now available on STN Easy
 NEWS  6  NOV 26  Two new SET commands increase convenience of STN
                  searching
 NEWS  7  DEC 01  ChemPort single article sales feature unavailable
 NEWS  8  DEC 12  GBFULL now offers single source for full-text
                  coverage of complete UK patent families
 NEWS  9  DEC 17  Fifty-one pharmaceutical ingredients added to PS
 NEWS 10  JAN 06  The retention policy for unread STNmail messages
                  will change in 2009 for STN-Columbus and STN-Tokyo
 NEWS 11  JAN 07  WPIDS, WPINDEX, and WPIX enhanced Japanese Patent
                  Classification Data

 NEWS EXPRESS JUNE 27 08 CURRENT WINDOWS VERSION IS V8.3,
              AND CURRENT DISCOVER FILE IS DATED 23 JUNE 2008.

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* * * * * * * * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 17:31:59 ON 16 JAN 2009

=> file uspatall

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	0.22	0.22

Jagoe

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FILE 'USPATFULL' ENTERED AT 17:32:24 ON 16 JAN 2009
CA INDEXING COPYRIGHT (C) 2009 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPATOLD' ENTERED AT 17:32:24 ON 16 JAN 2009
CA INDEXING COPYRIGHT (C) 2009 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPAT2' ENTERED AT 17:32:24 ON 16 JAN 2009
CA INDEXING COPYRIGHT (C) 2009 AMERICAN CHEMICAL SOCIETY (ACS)

=> s endothelial cell derived nitric oxide synthase
L1            2 ENDOTHELIAL CELL DERIVED NITRIC OXIDE SYNTHASE

=> s endothelial (s) nitric oxide synthase
L2         2641 ENDOTHELIAL (S) NITRIC OXIDE SYNTHASE

=> s enos
L3         2407 ENOS

=> s l1 or l2 or l3
L4         4256 L1 OR L2 OR L3

=> s thrombosis or thrombotic or platelet aggregate or clot or thrombi or embolism or
embolus
L5        71645 THROMBOSIS OR THROMBOTIC OR PLATELET AGGREGATE OR CLOT OR THROMB
                I OR EMBOLISM OR EMBOLUS

=> s l4 and l5
L6         1678 L4 AND L5

=> s inhibit? (s) syk
L7          825 INHIBIT? (S) SYK

=> s inhibit? (s) syk kinase
L8          243 INHIBIT? (S) SYK KINASE

=> s l8 and l6
L9            3 L8 AND L6

=> s l7 and l6
L10           9 L7 AND L6

=> dup rem
ENTER L# LIST OR (END):l10
PROCESSING COMPLETED FOR L10
L11           9 DUP REM L10 (0 DUPLICATES REMOVED)

=> d l11 1-9 ibib, kwic, ind

L11  ANSWER 1 OF 9  USPATFULL on STN
ACCESSION NUMBER:       2008:73661  USPATFULL
TITLE:                  SUBSTITUTED SULPHOXIMINES AS TIE2 INHIBITORS AND SALTS
                        THEREOF, PHARMACEUTICAL COMPOSITIONS COMPRISING SAME,
                        METHODS OF PREPARING SAME AND USES OF SAME
INVENTOR(S):            Hartung, Ingo, Berlin, GERMANY, FEDERAL REPUBLIC OF
                        Kettschau, Georg, Berlin, GERMANY, FEDERAL REPUBLIC OF
                        Briem, Hans, Bremen, GERMANY, FEDERAL REPUBLIC OF
                        Thierauch, Karl-Heinz, Berlin, GERMANY, FEDERAL
                        REPUBLIC OF
                        Luecking, Ulrich, Berlin, GERMANY, FEDERAL REPUBLIC OF
                        Boemer, Ulf, Glienicke/Nordbahn, GERMANY, FEDERAL
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10537599

REPUBLIC OF
Krueger, Martin, Berlin, GERMANY, FEDERAL REPUBLIC OF

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20080064696	A1	20080313
APPLICATION INFO.:	US 2007-776231	A1	20070711 (11)

	NUMBER	DATE
PRIORITY INFORMATION:	EP 2006-90121	20060712
	US 2006-831197P	20060717 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MILLEN, WHITE, ZELANO & BRANIGAN, P.C., 2200 CLARENDON BLVD., SUITE 1400, ARLINGTON, VA, 22201, US
NUMBER OF CLAIMS: 32
EXEMPLARY CLAIM: 1
LINE COUNT: 3915
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . ShcA to Y1102 of the Tie2 C-tail is also believed to induce cellular sprouting and motility effects involving activation of **endothelial nitric oxide synthase** (**eNOS**), focal adhesion kinase (FAK) and the GTPases RhoA and Rac1. Other downstream mediators of Tie2 signalling include the adaptor protein. . .

SUMM . . . derivatives have been frequently described as therapeutic agents for diverse diseases. Various recently published patent applications describe their use as **inhibitors** of protein kinases, for example in WO2001064654 and WO 2002096888 for use as CDK **inhibitors**, in WO 2003032997 for use as CDK and Aurora A kinase **inhibitors**, in WO 2003063794 for use as **Syk** kinase **inhibitors**, in WO 2003078404 for use as ZAP-70 and/or **Syk** or FAK kinase **inhibitors**, in WO 2004074244 for use as PLK **inhibitors**, in WO 2005026158 as ZAP-70 and/or **Syk** kinase **inhibitors**, and in WO 2005026130 as Alk **inhibitors**.

IT **Embolism**
(cerebral thromboembolism; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)

INCL INCLM: 514/235.800
INCLS: 514/252.130; 514/272.000; 514/275.000; 544/122.000; 544/295.000; 544/297.000; 544/321.000
NCL NCLM: 514/235.800
NCLS: 514/252.130; 514/272.000; 514/275.000; 544/122.000; 544/295.000; 544/297.000; 544/321.000
IC IPCI C07D0239-28 [I,A]; C07D0239-00 [I,C*]; A61K0031-496 [I,A]; A61K0031-505 [I,A]; A61K0031-5377 [I,A]; A61K0031-5375 [I,C*]; C07D0403-12 [I,A]; C07D0403-00 [I,C*]; C07D0413-12 [I,A]; C07D0413-00 [I,C*]; A61P0019-00 [I,A]; A61P0035-00 [I,A]; A61P0009-00 [I,A]
IPCR C07D0239-00 [I,C]; C07D0239-28 [I,A]; A61K0031-496 [I,C]; A61K0031-496 [I,A]; A61K0031-505 [I,C]; A61K0031-505 [I,A]; A61K0031-5375 [I,C]; A61K0031-5377 [I,A]; A61P0009-00 [I,C]; A61P0009-00 [I,A]; A61P0019-00 [I,C]; A61P0019-00 [I,A]; A61P0035-00 [I,C]; A61P0035-00 [I,A]; C07D0403-00 [I,C]; C07D0403-12 [I,A]; C07D0413-00 [I,C]; C07D0413-12 [I,A]

	PATENT	KIND	DATE
OS	CA 148:168740 * WO 2008006560	A1	20080117

* CA Indexing for this record included

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1

ST pyrimimidine aryl sulfoximine deriv prepn Tie2 inhibitor

IT Angiogenesis
(- dependent eye diseases; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)

IT Brain, neoplasm
(-associated edema; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)

IT Disease, animal
(accompanied with dysregulated vascular growth; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)

IT Respiratory distress syndrome
(adult; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)

IT Retinal disease
(age-related macular degeneration; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)

IT Inflammation
(angiogenesis-associated; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)

IT Eye, disease
(angiogenesis-dependent; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)

IT Prostate gland, disease
(benign hyperplasia; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)

IT Hyperplasia
(benign prostatic; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)

IT Edema
(brain tumor-associated; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)

IT Edema
(burn-induced; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)

IT **Embolism**
(cerebral thromboembolism; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)

IT Edema
(cerebral, hypoxia-induced; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of

diseases- accompanied with dysregulated vascular growth)
IT Lung, disease
(chronic; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)
IT Dermatitis
(contact; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)
IT Transplant and Transplantation
(cornea, rejection; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)
IT Eye
(cornea, transplant, rejection; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)
IT Transplant rejection
(corneal; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)
IT Allergy
(delayed hypersensitivity; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)
IT Brain, disease
(edema, hypoxia-induced; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)
IT Lung, disease
(edema; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)
IT Uterus, disease
(endometriosis; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)
IT Wound healing
(for reduction of scar formation during regeneration of damaged nerves; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)
IT Eye, disease
(macular edema; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)
IT Neoplasm
(metastasis; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)
IT Disease, animal
(of dysregulated vascular growth; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)
IT Artery, disease
(peripheral; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)
IT Hemorrhage
(postmenopausal; substituted sulfoximine as Tie2 inhibitors useful in

treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)
IT Disease, animal
(proliferative, benign; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)
IT Edema
Hypertension
(pulmonary; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)
IT Brain, disease
(stroke; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)
IT Aging, animal
Allergy inhibitors
Angiogenesis inhibitors
Anti-inflammatory agents
Antiasthmatics
Antihypertensives
Antirheumatic agents
Antitumor agents
Ascites
Asthma
Bone resorption
Bone resorption inhibitors
Coronary artery disease
Coronary restenosis
Cytotoxic agents
Diuretics
Edema
Immunosuppressants
Intestine, disease
Multiple sclerosis
Myoma
Neoplasm
Nervous system agents
Ovulation induction
Pharmaceutical carriers
Preeclampsia
Psoriasis
Respiratory system agents
Retinal disease
Rheumatoid arthritis
Signal transduction, biological
Vascular restenosis
Wound healing promoters
(substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)
IT Edema
(trauma-induced; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)
IT Altitude sickness
(trauma; substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)
IT 1002358-28-2P 1002358-29-3P 1002358-30-6P 1002358-31-7P

1002358-32-8P 1002358-33-9P 1002358-34-0P 1002358-35-1P
1002358-36-2P 1002358-37-3P 1002358-38-4P 1002358-39-5P
1002358-40-8P 1002358-41-9P 1002358-42-0P 1002358-43-1P
1002358-44-2P 1002358-45-3P 1002358-46-4P 1002358-47-5P
1002358-48-6P 1002358-49-7P 1002358-51-1P 1002358-53-3P
1002358-54-4P 1002358-55-5P 1002358-56-6P 1002358-57-7P
1002358-58-8P 1002358-59-9P 1002358-60-2P 1002358-61-3P
1002358-62-4P 1002358-63-5P 1002358-64-6P 1002358-65-7P
(preparation of arylpyrimidines derivs. containing sulfoximine functional group as Tie2 inhibitors)

IT 1002357-45-0P 1002357-57-4P 1002357-69-8P 1002358-06-6P
(preparation of arylpyrimidines derivs. containing sulfoximine functional group as Tie2 inhibitors)

IT 1002357-46-1P 1002357-48-3P 1002357-49-4P 1002357-50-7P
1002357-51-8P 1002357-53-0P 1002357-55-2P 1002357-58-5P
1002357-59-6P 1002357-60-9P 1002357-62-1P 1002357-64-3P
1002357-66-5P 1002357-67-6P 1002357-70-1P 1002357-71-2P
1002357-72-3P 1002357-74-5P 1002357-76-7P 1002357-77-8P
1002357-79-0P 1002357-81-4P 1002357-82-5P 1002357-83-6P
1002357-85-8P 1002357-86-9P 1002357-88-1P 1002357-89-2P
1002357-90-5P 1002357-91-6P 1002357-92-7P 1002357-93-8P
1002357-94-9P 1002357-95-0P 1002357-96-1P 1002357-97-2P
1002357-99-4P 1002358-01-1P 1002358-03-3P 1002358-05-5P
1002358-07-7P 1002358-08-8P 1002358-09-9P 1002358-10-2P
1002358-11-3P 1002358-12-4P 1002358-13-5P 1002358-14-6P
1002358-15-7P
(preparation of arylpyrimidines derivs. containing sulfoximine functional group as Tie2 inhibitors)

IT 22133-02-4P 1002358-27-1P
(preparation of arylpyrimidines derivs. containing sulfoximine functional group as Tie2 inhibitors)

IT 64-04-0, Benzeneethanamine 76-09-5, Pinacol 98-09-9, Benzenesulfonyl chloride 103-71-9, Phenyl isocyanate, reactions 108-00-9 123-00-2, 4-Morpholinepropanamine 329-01-1, 1-Isocyanato-3-trifluoromethylbenzene 367-24-8, 4-Bromo-2-fluoroaniline 535-52-4, 2-Fluoro-5-trifluoromethylaniline 541-41-3, Ethyl chloroformate 617-89-0, 2-Furanmethanamine 696-07-1, 5-Iodouracil 934-98-5 1795-48-8, Isopropyl isocyanate 2038-03-1, 4-Morpholineethanamine 2450-71-7, 2-Propyn-1-amine 2524-76-7 6120-95-2, 1-Phenylcyclopropanecarboxylic acid 7154-73-6, 1-Pyrrolidineethanamine 35320-23-1 36082-50-5, 5-Bromo-2,4-dichloropyrimidine 57054-92-9 73183-34-3 82417-45-6, 2,3-Dichlorobenzenesulfonyl chloride 104173-41-3 214360-73-3, 4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)phenylamine 1002358-26-0
(preparation of arylpyrimidines derivs. containing sulfoximine functional group as Tie2 inhibitors)

IT 3272-42-2P 13544-44-0P 59549-51-8P 209958-42-9P 218301-87-2P
262444-42-8P 796967-48-1P 819056-67-2P 819058-34-9P 851008-60-1P
851008-66-7P 912675-26-4P 912675-28-6P 914606-88-5P 939807-34-8P
942410-47-1P 942410-78-8P 942410-79-9P 942411-15-6P 942411-17-8P
942411-18-9P 960624-59-3P 1002358-16-8P 1002358-17-9P
1002358-18-0P 1002358-19-1P 1002358-20-4P 1002358-21-5P
1002358-22-6P 1002358-23-7P 1002358-24-8P 1002358-25-9P
(preparation of arylpyrimidines derivs. containing sulfoximine functional group as Tie2 inhibitors)

IT 148047-29-4, Tie-2 kinase
(substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)

IT 146279-89-2

(substituted sulfoximine as Tie2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases- accompanied with dysregulated vascular growth)

L11 ANSWER 2 OF 9 USPATFULL on STN

ACCESSION NUMBER:	2008:58493 USPATFULL
TITLE:	98 Human Secreted Proteins
INVENTOR(S):	Komatsoulis, George A., Silver Spring, MD, UNITED STATES Rosen, Craig A., Laytonsville, MD, UNITED STATES Ruben, Steven M., Brookeville, MD, UNITED STATES Duan, Roxanne D., Bethesda, MD, UNITED STATES Moore, Paul A., North Bethesda, MD, UNITED STATES Shi, Yanggu, Gaithersburg, MD, UNITED STATES LaFleur, David W., Washington, DC, UNITED STATES Wei, Ying-Fei, Berkeley, CA, UNITED STATES Ni, Jian, Germantown, MD, UNITED STATES Florence, Kimberly A., Rockville, MD, UNITED STATES Young, Paul E., Gaithersburg, MD, UNITED STATES Brewer, Laurie A., Eagan, MN, UNITED STATES Soppet, Daniel R., Centreville, VA, UNITED STATES Endress, Gregory A., Florence, MA, UNITED STATES Ebner, Reinhard, Gaithersburg, MD, UNITED STATES Olsen, Henrik, Gaithersburg, MD, UNITED STATES Mucenski, Michael, Cincinnati, OH, UNITED STATES
PATENT ASSIGNEE(S):	Human Genome Sciences, Inc., Rockville, MD, UNITED STATES, 20850 (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20080051338	A1	20080228
APPLICATION INFO.:	US 2007-777133	A1	20070712 (11)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2005-229769, filed on 20 Sep 2005, PENDING Continuation of Ser. No. US 2002-233453, filed on 4 Sep 2002, ABANDONED Division of Ser. No. US 2000-489847, filed on 24 Jan 2000, GRANTED, Pat. No. US 6476195 Continuation-in-part of Ser. No. WO 1999-US17130, filed on 29 Jul 1999, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-94657P	19980730 (60)
	US 1998-95486P	19980805 (60)
	US 1998-96319P	19980812 (60)
	US 1998-95454P	19980806 (60)
	US 1998-95455P	19980806 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	HUMAN GENOME SCIENCES INC., INTELLECTUAL PROPERTY DEPT., 14200 SHADY GROVE ROAD, ROCKVILLE, MD, 20850, US
NUMBER OF CLAIMS:	20
EXEMPLARY CLAIM:	1
NUMBER OF DRAWINGS:	3 Drawing Page(s)
LINE COUNT:	20515

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, myocardial infarction, myocarditis, ischemia, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis; pulmonary edema and

embolism, bronchitis and/or cystic fibrosis; Crohn's disease and/or colon cancer. Similarly, the tissue distribution indicates that polynucleotides and polypeptides corresponding to. . .

DETD . . . and rhabdomyosarcoma), as well as cardiovascular and respiratory or pulmonary disorders such as asthma, pulmonary edema, pneumonia, atherosclerosis, restenosis, stoke, **thrombosis** hypertension, inflammation and wound healing. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for. . .

DETD . . . prevention and/or diagnosis of cardiovasular and respiratory or pulmonary disorders such as asthma, pulmonary edema, pneumonia, atherosclerosis, restenosis, stoke, angina, **thrombosis**, hypertension, inflammation, and wound healing.

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies,. . .

DETD . . . of vascular conditions, which include, but are not limited to, microvascular disease, vascular leak syndrome, aneurysm, stroke, atherosclerosis, arteriosclerosis, or **embolism**. For example, this gene product may represent a soluble factor produced by smooth muscle that regulates the innervation of organs. . .

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies,. . .

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis.

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. The gene product may also be involved in lymphopoiesis, therefore, it can be used. . .

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies,. . .

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies,. . .

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies,. . .

DETD . . . the cell surface. The aggregation of FcR having immunoreceptor tyrosine-based activation motifs (ITAMs) activates sequentially src

family tyrosine kinases and **syk** family tyrosine kinases that connect transduced signals to common activation pathways shared with other receptors. FcR with ITAMs elicit cell. . . ITAM as signal transduction subunits. The coaggregation of antigen receptors or of FcR having ITAMs with FcR having immunoreceptor tyrosine-based **inhibition** motifs (ITIMs) negatively regulates cell activation. FcR therefore appear as the subunits of multichain receptors whose constitution is not predetermined. . .

DETD . . . gene or gene product may also useful in the treatment and/or detection of pulmonary defects such as pulmonary edema and **embolism**, bronchitis and cystic fibrosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue. . .

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Polynucleotides and polypeptides of the invention are also useful for the treatment, detection, and/or. . .

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies,. . .

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies,. . .

DETD . . . No. WO 97/34911), Fas Ligand (Takahashi et al., Int. Immunol., 6:1567-1574 (1994)), VEGI (See, International Publication No. WO 99/23105), a **thrombotic** agent or an anti-angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"),. . .

DETD . . . limited to, acidic and basic fibroblast growth factors, VEGF-1, VEGF-2 (VEGF-C), VEGF-3 (VEGF-B), epidermal growth factor alpha and beta, platelet-derived **endothelial** cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin like growth factor, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and **nitric oxide synthase**.

DETD . . . or antagonists of the present invention could also be used to modulate hemostatic (the stopping of bleeding) or thrombolytic activity (**clot** formation). For example, by increasing hemostatic or thrombolytic activity, a polynucleotides or polypeptides, or agonists or antagonists of the present. . .

DETD Myocardial ischemias include coronary disease, such as angina pectoris, coronary aneurysm, coronary arteriosclerosis, coronary **thrombosis**, coronary vasospasm, myocardial infarction and myocardial stunning.

DETD . . . Arteritis, aortitis, Leriche's Syndrome, arterial occlusive diseases, arteritis, enarteritis, polyarteritis nodosa, cerebrovascular diseases, disorders, and/or conditions, diabetic angiopathies, diabetic retinopathy, **embolisms**, **thrombosis**, erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension, ischemia, peripheral vascular diseases, phlebitis, pulmonary veno-occlusive disease, Raynaud's disease, CREST syndrome, retinal. .

.

DETD . . . include carotid artery diseases, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformation, cerebral artery diseases, cerebral **embolism** and **thrombosis**, carotid artery **thrombosis**, sinus **thrombosis**, Wallenberg's syndrome, cerebral hemorrhage, epidural hematoma, subdural hematoma, subaraxhnoid hemorrhage, cerebral infarction, cerebral ischemia (including transient), subclavian steal syndrome, periventricular. . .

DETD **Embolisms** include air **embolisms**, amniotic fluid **embolisms**, cholesterol **embolisms**, blue toe syndrome, fat **embolisms**, pulmonary **embolisms**, and thromoboembolisms. **Thrombosis** include coronary **thrombosis**, hepatic vein **thrombosis**, retinal vein occlusion, carotid artery **thrombosis**, sinus **thrombosis** , Wallenberg's syndrome, and thrombophlebitis.

DETD . . . cell growth, may be employed in treatment for stimulating re-vascularization of ischemic tissues due to various disease conditions such as **thrombosis**, arteriosclerosis, and other cardiovascular conditions. These polypeptide may also be employed to stimulate angiogenesis and limb regeneration, as discussed above.

INCL INCLM: 514/012.000
INCLS: 435/320.100; 435/325.000; 435/455.000; 435/006.000; 435/069.100; 435/007.100; 514/044.000; 530/350.000; 530/387.900; 536/023.500

NCL NCLM: 514/012.000
NCLS: 435/006.000; 435/007.100; 435/069.100; 435/320.100; 435/325.000; 435/455.000; 514/044.000; 530/350.000; 530/387.900; 536/023.500

IC IPCI A61K0031-70 [I,A]; A61K0038-00 [I,A]; C07K0014-00 [I,A]; C07K0016-18 [I,A]; C12N0015-00 [I,A]; C12N0015-11 [I,A]; C12N0015-87 [I,A]; C12N0005-06 [I,A]; C12P0021-04 [I,A]; C12Q0001-68 [I,A]; G01N0033-53 [I,A]

IPCR A61K0031-70 [I,C]; A61K0031-70 [I,A]; A61K0038-00 [I,C]; A61K0038-00 [I,A]; C07K0014-00 [I,C]; C07K0014-00 [I,A]; C07K0016-18 [I,C]; C07K0016-18 [I,A]; C12N0005-06 [I,C]; C12N0005-06 [I,A]; C12N0015-00 [I,C]; C12N0015-00 [I,A]; C12N0015-11 [I,C]; C12N0015-11 [I,A]; C12N0015-87 [I,C]; C12N0015-87 [I,A]; C12P0021-04 [I,C]; C12P0021-04 [I,A]; C12Q0001-68 [I,C]; C12Q0001-68 [I,A]; G01N0033-53 [I,C]; G01N0033-53 [I,A]

CHEMICAL ABSTRACTS INDEXING COPYRIGHT 2009 ACS on STN

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      CA 131:166245   WO      9943693  A1  19990902
      CA 131:210084   WO      9946289  A1  19990916
* CA Indexing for this record included
CC    3-3 (Biochemical Genetics)
       Section cross-reference(s): 6, 13, 15, 63
ST    human protein cDNA sequence
IT    Proteins, specific or class
        (ADF (adipocyte differentiation factor); cloning and cDNA sequences of
        human proteins)
IT    Proteins, specific or class
        (AIF-2 (allograft inflammatory factor-2); cloning and cDNA sequences of
        human proteins)
IT    Proteins, specific or class
        (AIF-3 (allograft inflammatory factor-3); cloning and cDNA sequences of
        human proteins)
IT    Proteins, specific or class
        (BEF (brain-enriched hyaluronan-binding factor); cloning and cDNA
        sequences of human proteins)
IT    Proteins, specific or class
        (Bcl-like; cloning and cDNA sequences of human proteins)
IT    Chemokines
        (CAT-1 (chemokine from activated T cell-1); cloning and cDNA sequences
        of human proteins)
IT    Chemokines
        (CAT-2 (chemokine from activated T cell-2); cloning and cDNA sequences
        of human proteins)
IT    Cytokines
        (CCV (chemotactic cytokine V); cloning and cDNA sequences of human
        proteins)
IT    Proteins, specific or class
        (ES/130-like I; cloning and cDNA sequences of human proteins)
IT    Proteins, specific or class
        (MIA-2 (melanoma inhibitory activity-2); cloning and cDNA sequences of
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human proteins)
IT Proteins, specific or class
(MIA-3 (melanoma inhibitory activity-3); cloning and cDNA sequences of human proteins)
IT Molecular cloning
(cloning and cDNA sequences of human proteins)
IT Antibodies
(cloning and cDNA sequences of human proteins)
IT Annexins
(cloning and cDNA sequences of human proteins)
IT cDNA sequences
(for human proteins)
IT Protein sequences
(of human proteins)
IT 208668-53-5P 210350-51-9P 210478-73-2P 210478-75-4P 210478-81-2P
210478-87-8P 210478-89-0P 210478-91-4P, Annexin (human clone HSAAL25)
210478-94-7P 210478-96-9P 210478-98-1P, Protein (human clone HAICH28
Bcl-like) 210478-99-2P 210479-00-8P 210488-21-4P 210488-27-0P
(amino acid sequence; cloning and cDNA sequences of human proteins)
IT 210478-61-8P 210478-74-3P 210478-76-5P 210478-84-5P 210478-85-6P
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210478-95-8P 210478-97-0P
(nucleotide sequence; cloning and cDNA sequences of human proteins)

L11 ANSWER 3 OF 9 USPATFULL on STN
ACCESSION NUMBER: 2008:44859 USPATFULL
TITLE: SULFONAMIDO-MACROCYCLES AS TIE2 INHIBITORS AND SALTS THEREOF, PHARMACEUTICAL COMPOSITIONS COMPRISING SAME, METHODS OF PREPARING SAME AND USES OF SAME
INVENTOR(S): Hartung, Ingo, Berlin, GERMANY, FEDERAL REPUBLIC OF
Briem, Hans, Bremen, GERMANY, FEDERAL REPUBLIC OF
Kettschau, Georg, Berlin, GERMANY, FEDERAL REPUBLIC OF
Thierauch, Karl-Heinz, Berlin, GERMANY, FEDERAL REPUBLIC OF
Luecking, Ulrich, Berlin, GERMANY, FEDERAL REPUBLIC OF
Boemer, Ulf, Glienicke/Nordbahn, GERMANY, FEDERAL REPUBLIC OF
Schaefer, Martina, Berlin, GERMANY, FEDERAL REPUBLIC OF
Lienau, Philip, Berlin, GERMANY, FEDERAL REPUBLIC OF

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20080039482	A1	20080214
APPLICATION INFO.:	US 2007-765674	A1	20070620 (11)

	NUMBER	DATE
PRIORITY INFORMATION:	EP 2006-90115	20060621
	US 2006-816640P	20060627 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: MILLEN, WHITE, ZELANO & BRANIGAN, P.C., 2200 CLARENDON BLVD., SUITE 1400, ARLINGTON, VA, 22201, US
NUMBER OF CLAIMS: 24
EXEMPLARY CLAIM: 1
LINE COUNT: 2642
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . ShcA to Y1102 of the Tie2 C-tail is also believed to induce cellular sprouting and motility effects involving activation of **endothelial nitric oxide synthase**

(**eNOS**), focal adhesion kinase (FAK) and the GTPases RhoA and Rac1. Other downstream mediators of Tie2 signalling include the adaptor protein. . .

SUMM . . . derivatives have been frequently described as therapeutic agents for diverse diseases. Various recently published patent applications describe their use as **inhibitors** of protein kinases, for example in WO2001064654 and WO 2002096888 for use as CDK **inhibitors**, in WO 2003032997 for use as CDK and Aurora A kinase **inhibitors**, in WO 2003063794 for use as **Syk** kinase **inhibitors**, in WO 2003078404 for use as ZAP-70 and/or **Syk** or FAK kinase **inhibitors**, in WO 2004074244 for use as PLK **inhibitors**, in WO 2005026158 as ZAP-70 and/or **Syk** kinase **inhibitors**, and in WO 2005026130 as Alk **inhibitors**.

IT **Embolism**
(cerebral thromboembolism, treatment of; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

INCL INCLM: 514/267.000
INCLS: 540/469.000

NCL NCLM: 514/267.000
NCLS: 540/469.000

IC IPCI A61K0031-519 [I,A]; A61P0035-00 [I,A]; A61P0009-00 [I,A]; C07D0513-02 [I,A]; C07D0513-00 [I,C*]
IPCR A61K0031-519 [I,C]; A61K0031-519 [I,A]; A61P0009-00 [I,C]; A61P0009-00 [I,A]; A61P0035-00 [I,C]; A61P0035-00 [I,A]; C07D0513-00 [I,C]; C07D0513-02 [I,A]

CHEMICAL ABSTRACTS INDEXING COPYRIGHT 2009 ACS on STN

	PATENT	KIND	DATE
OS CA 148:79078	* WO 2007147574	A1	20071227

* CA Indexing for this record included

CC 28-23 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 63

ST sulfonamido macrocycle prepn Tie2 inhibitor; treatment dysregulated vascular growth disease sulfonamido macrocycle prepn

IT Angiogenesis
(- dependent eye diseases, treatment of; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Disease, animal
(accompanied with dysregulated vascular growth, treatment of; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Respiratory distress syndrome
(adult, treatment of; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Retinal disease
(age-related macular degeneration, treatment of; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Inflammation
(angiogenesis-associated, treatment of; preparation of sulfonamidomacrocycles

as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Eye, disease
(angiogenesis-dependent, treatment of; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Prostate gland, disease
(benign hyperplasia, treatment of; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Hyperplasia
(benign prostatic, treatment of; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Edema
(brain tumor-associated, treatment of; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Edema
(burn-induced, treatment of; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT **Embolism**
(cerebral thromboembolism, treatment of; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Edema
(cerebral, hypoxia-induced, treatment of; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Lung, disease
(chronic, treatment of; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Dermatitis
(contact, treatment of; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Transplant and Transplantation
(cornea, rejection, treatment of; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Eye
(cornea, transplant, rejection, treatment of; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Transplant rejection
(corneal, treatment of; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Allergy

(delayed hypersensitivity, treatment of; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Brain, disease
(edema, hypoxia-induced, treatment of; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Lung, disease
(edema, treatment of; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Uterus, disease
(endometriosis, treatment of; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Eye, disease
(macular edema, treatment of; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Neoplasm
(metastasis, treatment of; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Disease, animal
(of dysregulated vascular growth, treatment of; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Artery, disease
(peripheral, treatment of; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Hemorrhage
(postmenopausal, treatment of; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Allergy inhibitors
Angiogenesis inhibitors
Anti-inflammatory agents
Antiasthmatics
Antihypertensives
Antirheumatic agents
Antitumor agents
Bone resorption inhibitors
Cytotoxic agents
Diuretics
Immunosuppressants
Nervous system agents
Pharmaceutical carriers
Respiratory system agents
Signal transduction, biological
Wound healing promoters
(preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Disease, animal
(proliferative, benign, treatment of; preparation of sulfonamidomacrocycles

as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Edema
Hypertension
(pulmonary, treatment of; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Wound healing
(reduction of scar formation during regeneration of damaged nerves; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Brain, disease
(stroke, treatment of; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Altitude sickness
(trauma, treatment of; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Edema
(trauma-induced, treatment of; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT Aging, animal
Ascites
Asthma
Bone resorption
Coronary artery disease
Coronary restenosis
Edema
Intestine, disease
Multiple sclerosis
Myoma
Neoplasm
Ovulation induction
Preeclampsia
Psoriasis
Retinal disease
Rheumatoid arthritis
Vascular restenosis
(treatment of; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT 960624-36-6P 960624-37-7P 960624-38-8P 960624-39-9P 960624-40-2P
960624-41-3P 960624-42-4P 960624-43-5P 960624-44-6P 960624-45-7P
960624-46-8P 960624-47-9P 960624-48-0P 960624-49-1P
(drug candidate; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT 209958-42-9P 218301-87-2P 262444-42-8P 666719-27-3P 666719-49-9P
819058-34-9P 894772-82-8P 960619-83-4P 960624-50-4P 960624-51-5P
960624-52-6P 960624-53-7P 960624-54-8P 960624-55-9P 960624-56-0P
960624-57-1P 960624-58-2P 960624-59-3P 960624-60-6P 960624-61-7P
960624-62-8P
(intermediate; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

IT 146279-89-2 148047-29-4, Tie-2 kinase 444018-21-7, Aurora c
(preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)
IT 76-09-5, Pinacol 367-24-8, 4-Bromo-2-fluoroaniline 73183-34-3
138500-88-6, 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)benzylamine
214360-73-3, 4-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)aniline
666719-50-2 960619-97-0
(starting material; preparation of sulfonamidomacrocycles as Tie-2 inhibitors useful in treatment of diseases of dysregulated vascular growth or of diseases-accompanied with dysregulated vascular growth)

L11 ANSWER 4 OF 9 USPATFULL on STN
ACCESSION NUMBER: 2006:150950 USPATFULL
TITLE: Method for sustaining **enos** activity
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CAS INDEXING IS AVAILABLE FOR THIS PATENT.
TI Method for sustaining **enos** activity
AB The present invention is directed to methods for sustaining **eNOS** activity to **inhibit** platelet aggregation, **clot** retraction, and enhance fibrinolysis. One embodiment of the invention provides methods of treating **thrombosis** by **inhibiting** the activity of the **syk** kinase. Another embodiment provides assays for the discovery of improved compounds to treat **thrombosis**, by screening for compounds which sustain **eNOS** activity. Yet another embodiment provides assays for the discovery of improved compounds to treat **thrombosis**, by identifying **inhibitors** of calpain and IIbIIIa by screening for compounds which act through calpain or IIbIIIa to sustain **eNOS** activity. Yet another embodiment provides for enhancing fibrinolysis, by **inhibiting** the activity of the **syk** kinase or calpain.
SUMM The present application is directed to methods and kits for sustaining **eNOS** activity. These methods and kits can be used to treat **thrombosis** by inhibiting platelet aggregation and **clot** retraction, and enhancing fibrinolysis.
SUMM Intravascular **thrombosis** is one of the most frequent pathological events and a major cause of morbidity and mortality.

Critical steps in the. . . disruption, rupture, or erosion of artherosclerotic plaques with the formation of either partially or completely occlusive thrombus. Factors that stimulate **thrombosis** include vascular damage, stimulation of platelets, and activation of the coagulation cascade. Platelet adhesion to the exposed subendothelial surfaces of injured blood vessels, with subsequent platelet activation, and the resulting platelet-rich **clot** formation have been shown to be associated with various pathological conditions. The most prevalent vascular disease states are related to. . . atherosclerosis and arteriosclerosis, acute myocardial infarction, chronic stable angina, unstable angina. transient ischemic attacks and strokes, peripheral vascular disease, arterial **thrombosis**, preeclampsia, **embolism**, restenosis or abrupt closure following angioplasty, carotid endarterectomy, anastomosis of vascular grafts, and etc. These conditions represent a variety of. . .

SUMM . . . a number of biochemical changes that must be tightly regulated. Regulation of platelets ensures that the formation of a blood **clot** is of sufficient size to seal off the damaged area, preventing blood loss, while not disrupting blood flow to vital. . .

SUMM Platelet aggregation refers to the adherence of platelets to each other, typically at the site of blood vessel damage. **Clot** retraction describes the contractile ability of platelets to consolidate or shrink the size of the blood **clot** once it has formed. This process is thought to be important for both maintenance of the vasculature and also the subsequent manner in which the blood **clot** is removed once wound healing has finished. Fibrinolysis, also known as **clot** lysis, refers to the process through which **thrombi** dissolve, as a consequence of activation of the fibrinolytic system.

SUMM Platelet aggregation, **clot** retraction, and fibrinolysis are important parts of thrombus regulation.

SUMM . . . process for mammals such as man, inappropriate clotting can also lead to disease states. For example, a pathological process called **thrombosis** results when platelet aggregation and/or a fibrin **clot** blocks (i.e., occludes) a blood vessel. Arterial **thrombosis** may result in ischemic necrosis of the tissue supplied by the artery. When the **thrombosis** occurs in a coronary artery, a myocardial infarction or heart attack can result. A **thrombosis** occurring in a vein may cause tissues drained by the vein to become edematous and inflamed. **Thrombosis** of a deep vein may be complicated by a pulmonary **embolism**. Preventing or treating **clots** in a blood vessel may be therapeutically useful by inhibiting formation of blood **platelet aggregates**, inhibiting formation of fibrin, inhibiting thrombus formation, inhibiting **embolus** formation, and for treating or preventing unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, atrial fibrillation, **thrombotic** stroke, embolic stroke, deep vein **thrombosis**, disseminated intravascular coagulation, ocular build up of fibrin, and reocclusion or restenosis of recanalized vessels.

SUMM Nitric oxide (NO) plays an important role during thrombus formation. During platelet aggregation and **clot** retraction, both inducible **nitric oxide synthase** (NOS) and constitutive **nitric oxide synthase** (**eNOS**) are transiently activated and then deactivated. The activity of nitric oxide (NO) as a vasodilator has been known for well. . . (i) a constitutive, Ca++/calmodulin dependent enzyme, located in the endothelium, that releases NO in response to receptor or physical stimulation (**eNOS**); (ii) a constitutive, Ca++/calmodulin dependent enzyme, located in the brain, that releases NO in response to

receptor or physical stimulation; and (iii) a Ca++ independent enzyme which is induced after activation of vascular smooth muscle, macrophages, **endothelial** cells, and a number of other cells by endotoxin and cytokines (NOS). All three NOS isoforms have a similar molecular. . .

SUMM . . . coronary syndromes. More particularly, the ability to sustain NO production and release correlates with the inhibition of platelet aggregation and **clot** retraction.

SUMM . . . certain calpain inhibitors are useful as inhibitors against aggregation of platelets caused by thrombin. Similarly, inhibition of calpains for treating **thrombosis** or **thrombotic** platelet aggregation is described in U.S. patent application Ser. No. 09/847,872, filed May 2, 2001 and published as US 2002/0115665.. . . No. 6,448,245, issued Sep. 10, 2002, provides methods and compounds for inhibiting calpains. However, while activity has focused on inducing **nitric oxide synthase** activity, it has not been previously known how to regulate constitutive **endothelial nitric oxide synthase** (**eNOS**) activity.

SUMM . . . by an agonist such as thrombin, the GPIIb/IIIa binding site becomes available to fibrinogen, eventually resulting in platelet aggregation and **clot** formation. Thus, the surface integrin GPIIb/IIIa (also known as the platelet integrin α.sub.IIbβ.sub.3) plays a key role during platelet aggregation.

SUMM Anti-**thrombotic** agents can block or inhibit thrombus formation, as discussed above; however, they are not very effective in dissolving a pre-formed. . .

SUMM However, fibrinolytic agents typically have problems because of the inhibitory effect of platelets on **clot** lysis. Activated platelets at sites of thrombus secrete agents which inhibit proteolytic processing of plasminogen to active plasmin. The serpin. . . and Kluft, Blood: 69:381 (1987)] Several animal and clinical studies have associated elevations in plasma PAI-1 with increased risk for **thrombosis**, whereas a drop in plasma PAI-1 levels may be a cause of recurrent bleeding.

SUMM . . . latent or inactive form, suggesting its effect on fibrinolysis to be rather limited. Nevertheless, the inhibitory effect of platelets on **clot** lysis was proposed to be mediated partly by platelet PAI-1, a conclusion supported by differential **clot** lysis efficiency in the presence of normal platelets or platelets derived from PAI-1-deficient patients.

SUMM . . . the area of cardiovascular and cerebrovascular therapeutics for alternative agents which can be used in the prevention and treatment of **thrombi**. Accordingly, it would be desirable to have improved methods for treating **thrombosis**. More particularly, it would be desirable to have improved compounds to inhibit platelet aggregation and **clot** retraction, and promote fibrinolysis. There is also a need to have better assays for screening for such compounds.

SUMM The present invention provides methods and kits for sustaining constitutive **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and promote fibrinolysis. We have now shown that there are three different routes to sustain constitutive **eNOS** activity: (1) by **inhibiting** the activity of the **syk** kinase; (2) by **inhibiting** calpain; and (3) by using an antagonist of IIbIIIa.

SUMM One embodiment of the invention provides means for **inhibiting** the activity of the **syk** kinase. This can then be used to treat **thrombosis**.

SUMM Another embodiment of the present invention provides assays for the discovery of improved compounds to treat **thrombosis**, by screening for compounds which sustain constitutive **eNOS** activity.

SUMM Another embodiment of the present invention provides assays for the discovery of improved compounds to treat **thrombosis**, by identifying inhibitors of calpain and IIbIIIa by screening for compounds which act through calpain or IIbIIIa to sustain constitutive **eNOS** activity.

SUMM Yet another embodiment provides methods for treating or preventing **thrombosis** by promoting fibrinolysis by **inhibiting** the activity of the **syk** kinase or calpain.

DRWD FIG. 1 shows the effect of a **syk** kinase **inhibitor**, piceatannol, on **clot** retraction. Platelets (2+10.sup.8 platelets/ml) were incubated with either piceatannol at a final concentration of 40 μg/ml, calpeptin at a final. . . nM, 1 mM Ca.sup.2+, and 2 mM Mg.sup.2+, 10 minutes prior to the addition of 0.5 unit/ml of thrombin. The **clots** were incubated for 30 minutes at 37° C. and then transferred to ice before taking photographs. Tubes: 1, vehicle control. . .

DETD We have now discovered that sustaining constitutive **endothelial nitric oxide synthase** (**eNOS**) activity can be used to **inhibit** platelet aggregation and **clot** retraction, and/or to enhance fibrinolysis. During platelet aggregation and **clot** retraction, both inducible **nitric oxide synthase** (NOS) and constitutive **endothelial nitric oxide synthase** (**eNOS**) are transiently activated and then deactivated. While it was reported that calpeptin and IIbIIIa antagonists can **inhibit** inducible NOS, it was not known how to regulate constitutive **eNOS** activity. We have now found three different routes to sustain constitutive **eNOS** activity: (1) by **inhibiting** the activity of the **syk** kinase; (2) by **inhibiting** calpain; and (3) by using an antagonist of IIbIIIa.

DETD One embodiment of the invention provides methods of treating **thrombosis** by **inhibiting** the activity of the **syk** kinase. A second embodiment of the present invention provides assays for the discovery of improved compounds to treat **thrombosis**, by screening for compounds which sustain **eNOS** activity, preferably constitutive **eNOS** activity. A third embodiment of the present invention provides assays for the discovery of improved compounds to treat **thrombosis**, by identifying **inhibitors** of calpain and IIbIIIa by screening for compounds which act through calpain or IIbIIIa to sustain **eNOS** activity, preferably constitutive **eNOS**.

DETD . . . a critical physiological process for mammals such as man, and can also lead to disease states. A pathological process called **thrombosis** results when platelet aggregation and/or a fibrin **clot** blocks (i.e., occludes) a blood vessel. Arterial **thrombosis** may result in ischemic necrosis of the tissue supplied by the artery. When the **thrombosis** occurs in a coronary artery, a myocardial infarction or heart attack can result. A **thrombosis** occurring in a vein may cause tissues drained by the vein to become edematous and inflamed. **Thrombosis** of a deep vein may be complicated by a pulmonary **embolism**. Preventing or treating **clots** in a blood vessel may be therapeutically useful by inhibiting formation of blood **platelet aggregates**, inhibiting formation of fibrin, inhibiting thrombus formation, inhibiting **embolus** formation, and for treating or preventing unstable angina, refractory angina, myocardial infarction, transient

ischemic attacks, atrial fibrillation, **thrombotic** stroke, embolic stroke, deep vein **thrombosis**, disseminated intravascular coagulation, ocular build up of fibrin, and reocclusion or restenosis of recanalized vessels.

DETD One embodiment of the invention provides methods, kits, and compounds to sustain constitutive **eNOS** activity to inhibit platelet aggregation. Another embodiment of the invention provides methods, kits, and compounds to sustain constitutive **eNOS** activity to inhibit **clot** retraction. Yet another embodiment of the invention provides methods, kits, and compounds to sustain constitutive **eNOS** activity to promote fibrinolysis.

DETD . . . kits, compounds, and methods of the present invention can be used for the treatment and prevention of a variety of **thrombotic** conditions including coronary artery and cerebrovascular disease. The present invention can inhibit the formation of blood **platelet**, **aggregates**, inhibit the formation of fibrin, inhibit thrombus formation, and inhibit **embolus** formation in a mammal, in blood, in blood products, and in mammalian organs. The methods, kits, and compounds also can be used for treating or preventing unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, atrial fibrillation, **thrombotic** stroke, embolic stroke, deep vein **thrombosis**, disseminated intravascular coagulation, ocular build up of fibrin, and reocclusion or restenosis of recanalized vessels in a mammal. The methods,. . .

DETD . . . lung artery by a detached thrombus), cardiogenic thromboembolism (e.g. obstruction or occlusion of the heart by a detached thrombus), arterial **thrombosis** (e.g. formation of a thrombus within an artery that may cause infarction of tissue supplied by the artery), atherosclerosis (e.g.. . . irregularly distributed lipid deposits) in mammals, and for lowering the propensity of devices that come into contact with blood to **clot** blood.

DETD . . . may be treated or prevented with the present invention include obstruction of a vein, obstruction of a lung artery (pulmonary **embolism**), deep vein **thrombosis**, **thrombosis** associated with cancer and cancer chemotherapy, **thrombosis** inherited with thrombophilic diseases such as Protein C deficiency, Protein S deficiency, antithrombin III deficiency, and Factor V Leiden, and **thrombosis** resulting. from acquired thrombophilic disorders such as systemic lupus erythematosus (inflammatory connective tissue disease). Also with regard to venous thromboembolism,. . .

DETD Examples of arterial **thrombosis** which may be treated or prevented with the invention include unstable angina (severe constrictive pain in chest of coronary origin),. . . after percutaneous transluminal coronary angioplasty, occlusion of coronary artery bypass grafts, and occlusive cerebrovascular disease. Also with regard to arterial **thrombosis**, the invention is useful for maintaining patency in arteriovenous cannulas.

DETD The present invention is also useful for treating or preventing **thrombosis** associated with cancer and cancer chemotherapy in humans and other mammals.

DETD **Inhibition** of **Syk** Kinase

DETD One embodiment of the invention provides methods of treating **thrombosis** by **inhibiting** the activity of the **syk** kinase. As described above, **syk** is one of several cellular kinases activated during platelet activation, by directly associating with the integrin α.sub.IIbβ.sub.3 in platelets. We have now discovered that **eNOS** activity is sustained in the presence of **syk** **inhibitors**, for example piceatannol.

DETD One embodiment of the invention provides methods, kits, and compounds to sustain constitutive **eNOS** activity to **inhibit**

platelet aggregation by **inhibiting** the activity of the **syk** kinase. Another embodiment of the invention provides methods, kits, and compounds to sustain constitutive **eNOS** activity to **inhibit** **clot** retraction by **inhibiting** the activity of the **syk** kinase. Yet another embodiment of the invention provides methods, kits, and compounds to sustain constitutive **eNOS** activity to promote fibrinolysis by **inhibiting** the activity of the **syk** kinase.

DETD The activity of **syk** kinase can be **inhibited** using an agent that **inhibits** its function. One preferred **inhibitor** of **syk** is the plant natural product, piceatannol [Oliver, J. M. et al., J. Biol. Chem., 269: 29697-29703 (1994)]. Other **inhibitors** of **syk** are the pyrimidine-5-carboxamide derivatives described in U.S. Pat. No. 6,432,963. In one preferred embodiment, the **syk** kinase **inhibitor** is used to **inhibit** platelet aggregation and is not piceatannol.

DETD In one preferred embodiment, the **syk** **inhibitor** is a peptide **inhibitor**, as described in U.S. Pat. No. 5,858,981. The peptide **inhibitor** of the invention, or mimetic thereof, can be introduced into target cells directly, for example, using liposomes. See also approaches. . . peptides modified so as to render them capable of crossing cellular lipid membranes. Alternatively, a DNA sequence encoding the peptide **inhibitor** can be introduced using gene therapy protocols so that the peptide is produced intracellularly.

DETD Suitable **syk** **inhibitors** include specific **syk** **inhibitors**, **syk** interference RNA, antibodies to **syk** or antigenic fragments thereof, intrabodies against **syk** antisense oligonucleotides that **inhibit** **syk** expression and synthesis **syk** decoys such as dominant negative **syk** protein, and any organic or inorganic molecule designed to interfere with the activity of **syk**. Preferably one uses a single chain antibody as a **syk** **inhibitor**. One can also prepare or screen for other ligands that bind to **syk**.

DETD **syk** activity or function may also be **inhibited** using antisense nucleic acid technology. Antisense nucleic acids and oligonucleotides targeted against **syk**. useful according to the invention can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the. . .

DETD Compounds that **inhibit** **syk** can be formulated as pharmaceutical compositions and administered to a mammalian host, such as a human patient in a variety. . . of administration, i.e., orally or parenterally, by intravenous, intramuscular, topical or subcutaneous routes. The present invention also provides kits containing **syk** **inhibitors**.

DETD Discovery of Novel Compounds which Sustain **eNOS** Activity

DETD We have now discovered that sustaining **eNOS** activity is a potent anti-**thrombotic** treatment. Accordingly, the invention provides assays for the discovery of improved compounds to treat **thrombosis**, by screening for compounds which sustain **eNOS** activity. Preferably the **eNOS** activity sustained is constitutive **eNOS** activity.

DETD . . . in the art will also recognize that there are numerous other assays for the activity of the NOS isoforms (including **eNOS**) which can be used to screen the biological activity of the compounds to identify compounds which sustain **eNOS** activity. These include assays for native NOS isoforms in tissues studied ex vivo (Mitchell et al., Br. J. Pharmacol. (1991),. . . Commun. (1996), Vol. 219, pp.

359-365). Any of these heterologous expression systems can be used to establish iNOS, nNOS and **eNOS** assay systems to evaluate the biological activity of the compounds of the present invention.

DETD The effect of any compound identified as sustaining **eNOS** activity can be further characterized for its effect on platelet aggregation.

DETD . . . invention, a variety of test compounds from various sources can be screened for the ability of the compound to sustain **eNOS** activity. Compounds, to be screened can be naturally occurring or synthetic molecules. Compounds to be screened can also be obtained. . .

DETD Assays to Identify Calpain and IIb/IIIa Inhibitors which Sustain **eNOS** Activity

DETD Yet another embodiment of the present invention provides assays for the discovery of improved compounds to treat **thrombosis**, by identifying inhibitors of calpain and GPIIb/IIIa by screening for compounds which act through calpain or IIbIIIa to sustain **eNOS** activity, preferably constitutive **eNOS** activity.

DETD During platelet aggregation and **clot** retraction, both inducible **nitric oxide synthase** (NOS) and constitutive **endothelial nitric oxide synthase** (**eNOS**) are transiently activated and then deactivated. While it has been shown that calpeptin and IIbIIIa antagonists can inhibit inducible NOS, we have now discovered that such antagonists can also inhibit **eNOS**.

DETD Accordingly, one embodiment of the present invention provides for the development of assays to identify improved compounds to treat **thrombosis**, by identifying compounds which function via inhibition of calpain to sustain **eNOS** activity. Such assays comprise two steps: first, identifying inhibitors of calpain, and second, screening those inhibitors to identify those compounds that sustain **eNOS** activity.

DETD One embodiment of the invention provides methods, kits, and compounds to sustain constitutive **eNOS** activity to inhibit platelet aggregation by inhibiting the activity of calpain. Another embodiment of the invention provides methods, kits, and compounds to sustain constitutive **eNOS** activity to inhibit **clot** retraction by inhibiting the activity of calpain. Yet another embodiment of the invention provides methods, kits, and compounds to sustain constitutive **eNOS** activity to promote fibrinolysis by inhibiting the activity of calpain.

DETD . . . used to screen for compounds which inhibit its activity. Such inhibitors are then further characterized for the ability to sustain **eNOS** activity, as described above.

DETD Any compound which is identified as inhibiting calpain is then further screened for its ability to sustain **eNOS** activity, as described above.

DETD . . . test compounds from various sources can be screened for the ability of the compound to both inhibit calpain and sustain **eNOS** activity, as described above. Compounds to be screened can be naturally occurring or synthetic molecules. Compounds to be screened can. . .

DETD The present invention also provides for the development of assays to identify improved compounds to treat **thrombosis**, by identifying compounds which function via inhibition of GPIIb/IIIa to sustain **eNOS** activity. Such assays comprise a two steps: first, identifying inhibitors of GPIIb/IIIa, and second, screening those inhibitors to identify those compounds that sustain **eNOS** activity.

DETD One embodiment of the invention provides methods, kits, and compounds to sustain constitutive **eNOS** activity to inhibit platelet

aggregation by inhibiting IIb/IIIa. Another embodiment of the invention provides methods, kits, and compounds to sustain constitutive **eNOS** activity to inhibit **clot** retraction by inhibiting IIb/IIIa. Yet another embodiment of the invention provides methods, kits, and compounds to sustain constitutive **eNOS** activity to promote fibrinolysis by inhibiting IIb/IIIa.

DETD . . . used to screen for compounds which inhibit its activity. Such inhibitors are then further characterized for the ability to sustain **eNOS** activity, as described above.

DETD Any compound which is identified as inhibiting GPIIb/IIIa is then further screened for its ability to sustain **eNOS** activity, as described above.

DETD . . . test compounds from various sources can be screened for the ability of the compound to both inhibit GPIIb/IIa and sustain **eNOS** activity, as described above. Compounds to be screened can be naturally occurring or synthetic molecules. Compounds to be screened can. . .

DETD . . . above-described forms of the compound and a pharmaceutically acceptable carrier, including instructions for how to use it to sustain constitutive **eNOS** activity, which can then be used in treating or preventing the ailments described above.

DETD The present invention provides kits containing the compound and a pharmaceutically acceptable carrier, including the **syk inhibitors**, GPIIb/IIIa, or calpain **inhibitors**.

DETD Inhibition of **Clot** Retraction

DETD To determine the effect of the **syk** kinase **inhibitor** piceatannol and the calpain **inhibitor** calpeptin, the following experiments were carried out. Platelets (2+10.sup.8 platelets/ml) were incubated with either piceatannol at a final concentration of. . . nM, 1 mM Ca.sup.2+, and 2 mM Mg.sup.2+, 10 minutes prior to the addition of 0.5 unit/ml of thrombin. The **clots** were incubated for 30 minutes at 37° C. and then transferred to ice before taking photographs. Tubes: 1, vehicle control. . .

DETD Piceatannol at 20 ug/ml and 40 ug/ml **inhibited clot** retraction where as PP2 at 10 μM did not. As shown in FIG. 1, no **clot** retraction was observed in tube 1 when thrombin was not added which served as a negative control. Tube 2 showed a retracted **clot** which is like a small white thread hanging in the tube. Tubes 3 and 4 do not contain this retracted **clot**, suggesting that piceatannol at 40 ug/ml and calpeptin 200 ug/ml **inhibited** platelet mediated **clot** retraction. Results from other experiments showed that Piceatannol at 20 ug/ml was also able to **inhibit clot** retraction but 10 ug/ml piceatannol was not that effective (data not shown). 10 uM PP2, a specific **inhibitor** of src kinase did not have any effect on **clot** retraction (data not shown). This concentration of this **inhibitor** is reported to **inhibit** src kinase. Thus, piceatannol mediated **inhibition** of **clot** retraction seems due to the **inhibition** of **syk** kinase.

DETD This result indicates that piceatannol mediated **clot** retraction is due to **syk** kinase **inhibition** and not due to src kinase **inhibition** as src kinase specific **inhibitor** PP2 failed to show any **inhibition**. Calpeptin at 200 μg/ml **inhibited clot** retraction (FIG. 1), which shows that calpain **inhibition** also blocks **clot** retraction.

DETD . . . NO production (compare right panel with the left) from platelets at the same concentration it inhibits both platelet aggregation and **clot** retraction. We conclude that enhanced and sustained NO production by endothelial nitric oxide present in platelets

(**eNOS**) at least may be one of the reasons if not the sole reason for the inhibition platelet aggregation and **clot** retraction when calpain activation is inhibited.

DETD **Clot** lysis

DETD Anti-**thrombotic** agents can block or inhibit thrombus formation but they are not much effective on pre-formed thrombus to dissolve them and/or. . .

DETD First, we developed a retracted **clot** in the presence of fluorescence tagged fibrinogen in tubes containing platelets by the addition of thrombin. The residual fluid was. . . and put in separate microfuge tubes followed by centrifugation. The detection of fluorescence in the supernatant was a measure of **clot** lysis.

DETD Piceatannol at 40 μg/ml and calpeptin at 200 μg/ml increased fibrinolysis of **clots** made in the presence of platelets and lysis assay done in the presence of platelets, up to about 600% (6.2 times) of that of the control (Table 1). Normally, it is very difficult to achieve **clot** lysis in the presence of platelets. The control sample without treatment showed negligible **clot** lysis as expected. The value in control was designated as 1 to get comparative values for the treated samples.

TABLE 1

Clot Lysis in the Presence of Platelets

Control	1
Piceatannol 40 ug/ml	6.2
Calpeptin 200 ug/ml	6.2

DETD To form the **clot**, Oregon green 488 conjugated fibrinogen (fluorescent, from Molecular Probe) at 300 nM final concentration, 1 mM Ca.sup.2+, 2 mM M.sup.2+, was added to platelets at 2+10.sup.8/ml concentration in 0.5 ml. The **clot** retraction was started with the addition of 0.5 unit/ml thrombin. The tubes were kept at 37° C. in dark for 1 hour until the **clot** retraction was complete. The residual fluid was taken out from each tube.

DETD To initiate **clot** lysis, platelets at 2+10.sup.8/ml concentration were treated with either 40 ug/ml piceatannol, 200 ug/ml calpeptin or vehicle DMSO. In 0.25. . .

DETD This is the first demonstration of successful **clot** lysis in the presence of platelets. **Clot** lysis was obtained due to the **inhibition** of **syk** and protease calpain respectively. The mechanism of **inhibition** is under investigation. It is possible that the enhanced formation of plasmin from plasminogen by t-Pa may be facilitated by. . .

DETD Taken together, these results show that **inhibition** of either **syk** kinase or the protease calpain: (i) enhanced and sustained the production of NO in platelets; (ii) **inhibited** **clot** retraction; and (iii) enhanced **clot** lysis. Thus, **inhibition** of **syk** activation and calpain activation in platelets is useful for preventing **thrombotic** events as well as promoting fibrinolytic events.

CLM What is claimed is:

1. A method of treating **thrombotic** conditions in blood in a subject in need thereof comprising administering to the subject an **inhibitor** of **syk** kinase and a pharmaceutically acceptable carrier.

CLM What is claimed is:

2. The method of claim 1, wherein the **thrombotic** condition is

selected from the group consisting of thrombus formation, venous thromboembolism, pulmonary **embolism**, deep vein **thrombosis**, cardiogenic thromboembolism, thromboembolic stroke, and unstable angina.

CLM What is claimed is:
7. The method of claim 1 wherein one adds to blood a therapeutically effective amount of an **inhibitor** of **syk** kinase to **inhibit** formation of blood **platelet** **aggregates**
.

CLM What is claimed is:
9. A method of identifying a compound useful in the treatment of a **thrombotic** condition, comprising screening a library of candidate compounds to identify those compounds which sustain constitutive **eNOS** activity during platelet aggregation.

CLM What is claimed is:
. . . in a subject in need thereof comprising administering to the subject a compound selected from the group consisting of an **inhibitor** of **syk** kinase and an **inhibitor** of calpain, and a pharmaceutically acceptable carrier.

CLM What is claimed is:
25. The method of claim 24 wherein the compound is an **inhibitor** of **syk** kinase.

ST sustaining **eNOS** activity inhibition platelet aggregation; blood **clot** retraction inhibition sustaining **eNOS**; fibrinolysis enhancement sustaining **eNOS**; constitutive nitric oxide synthase **thrombosis** treatment; **syk** kinase **inhibitor** **thrombosis** treatment; calpain inhibitor **thrombosis** treatment; integrin IIbIIIa inhibitor **thrombosis** treatment; calpeptin nitric oxide prodn platelet aggregation inhibition

IT Heart, disease
(angina pectoris, unstable, treatment of; **inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)

IT Brain, disease
(embolic stroke, thromboembolic stroke, treatment of; **inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)

IT Lung, disease
(**embolism**, treatment of; **inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)

IT Anticoagulants
IT Drug delivery systems
IT Drug screening
IT Fibrinolysis
IT Platelet (blood)
IT Platelet aggregation
IT Platelet aggregation
IT Platelet aggregation **inhibitors**
IT Prophylaxis
IT Thrombolytics
IT Thrombus

(**inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)

IT Drug delivery systems
(kits; **inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)

IT **Embolism**
(pulmonary, treatment of; **inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)

IT Chemical library
(screening of; **inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)

IT **Embolism**
(thromboembolism, cardiogenic thromboembolism, treatment of; **inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)

IT **Embolism**
(thromboembolism, treatment of; **inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)

IT **Thrombosis**
(treatment of; **inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)

IT **Thrombosis**
(venous, treatment of; **inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)

IT Integrins
(αIIbβ3, **inhibitors**; **inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)

IT 117591-20-5, Calpeptin
(calpain **inhibitor**, **clot** retraction **inhibition** by; **inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)

IT 10102-43-9, Nitric oxide, biological studies
(calpeptin induction of platelet production of; **inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)

IT 503473-02-7, **ENOS**
(**inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)

IT 78990-62-2, Calpain 138674-26-7, **Syk** kinase
(**inhibitors**; **inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)

IT 10083-24-6, Piceatannol
(**syk** kinase **inhibitor**, **clot** retraction **inhibition** by; **inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)
INCL INCLM: 424/094.200
INCLS: 514/002.000
NCL NCLM: 424/094.200
NCLS: 514/002.000
IC IPCI A61K0038-54 [I,A]; A61K0038-43 [I,C*]
IPCR A61K0038-43 [I,C]; A61K0038-54 [I,A]

CHEMICAL ABSTRACTS INDEXING COPYRIGHT 2009 ACS on STN

	PATENT	KIND	DATE
OS CA 141:33803 *	WO 2004052364	A1	20040624

* CA Indexing for this record included
CC 1-8 (Pharmacology)
Section cross-reference(s): 7
ST sustaining **eNOS** activity inhibition platelet aggregation; blood **clot** retraction inhibition sustaining **eNOS**; fibrinolysis enhancement sustaining **eNOS**; constitutive nitric oxide synthase **thrombosis** treatment; **syk** kinase **inhibitor** **thrombosis** treatment; calpain inhibitor **thrombosis** treatment; integrin IIbIIIa inhibitor **thrombosis** treatment; calpeptin nitric oxide prodn platelet aggregation inhibition
IT Heart, disease
(angina pectoris, unstable, treatment of; **inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)
IT Brain, disease
(embolic stroke, thromboembolic stroke, treatment of; **inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)
IT Lung, disease
(**embolism**, treatment of; **inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)
IT Anticoagulants
Drug delivery systems
Drug screening
Fibrinolysis
Platelet (blood)
Platelet aggregation
Platelet aggregation
Platelet aggregation **inhibitors**
Prophylaxis
Thrombolytics
Thrombus
(**inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)
IT Drug delivery systems
(kits; **inhibitors** of calpain and **syk** kinase for

sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)

IT **Embolism**
(pulmonary, treatment of; **inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)

IT Chemical library
(screening of; **inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)

IT **Embolism**
(thromboembolism, cardiogenic thromboembolism, treatment of; **inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)

IT **Embolism**
(thromboembolism, treatment of; **inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)

IT **Thrombosis**
(treatment of; **inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)

IT **Thrombosis**
(venous, treatment of; **inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)

IT Integrins
(αIIbβ3, **inhibitors**; **inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)

IT 117591-20-5, Calpeptin
(calpain **inhibitor**, **clot** retraction **inhibition** by; **inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)

IT 10102-43-9, Nitric oxide, biological studies
(calpeptin induction of platelet production of; **inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)

IT 503473-02-7, **ENOS**
(**inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)

IT 78990-62-2, Calpain 138674-26-7, **Syk** kinase
(**inhibitors**; **inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance fibrinolysis)

IT 10083-24-6, Piceatannol
(**syk** kinase **inhibitor**, **clot** retraction **inhibition** by; **inhibitors** of calpain and **syk** kinase for sustaining **eNOS** activity to **inhibit** platelet aggregation and **clot** retraction and to enhance

fibrinolysis)

L11 ANSWER 5 OF 9 USPATFULL on STN
ACCESSION NUMBER: 2006:93539 USPATFULL
TITLE: 98 human secreted proteins
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PATENT ASSIGNEE(S): Human Genome Sciences, Inc., Rockville, MD, UNITED STATES (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20060079670	A1	20060413
APPLICATION INFO.:	US 2005-229769	A1	20050920 (11)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2002-233453, filed on 4 Sep 2002, ABANDONED Division of Ser. No. US 2000-489847, filed on 24 Jan 2000, GRANTED, Pat. No. US 6476195 Continuation-in-part of Ser. No. WO 1999-US17130, filed on 29 Jul 1999, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-94657P	19980730 (60)
	US 1998-95486P	19980805 (60)
	US 1998-96319P	19980812 (60)
	US 1998-95455P	19980806 (60)
	US 1998-95454P	19980806 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HUMAN GENOME SCIENCES INC, INTELLECTUAL PROPERTY DEPT., 14200 SHADY GROVE ROAD, ROCKVILLE, MD, 20850, US
NUMBER OF CLAIMS: 20
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Page(s)
LINE COUNT: 20543
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, myocardial infarction, myocarditis, ischemia, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis; pulmonary edema and **embolism**, bronchitis and/or cystic fibrosis; Crohn's disease and/or colon cancer. Similarly, the tissue distribution indicates that polynucleotides and polypeptides corresponding to. . .
DETD . . . and rhabdomyosarcoma), as well as cardiovascular and

respiratory or pulmonary disorders such as asthma, pulmonary edema, pneumonia, atherosclerosis, restenosis, stoke, **thrombosis** hypertension, inflammation and wound healing. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for. . .

DETD . . . prevention and/or diagnosis of cardiovasular and respiratory or pulmonary disorders such as asthma, pulmonary edema, pneumonia, atherosclerosis, restenosis, stoke, angina, **thrombosis**, hypertension, inflammation, and wound healing.

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies,. . .

DETD . . . of vascular conditions, which include, but are not limited to, microvascular disease, vascular leak syndrome, aneurysm, stroke, atherosclerosis, arteriosclerosis, or **embolism**. For example, this gene product may represent a soluble factor produced by smooth muscle that regulates the innervation of organs. . .

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies,. . .

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis.

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. The gene product may also be involved in lymphopoiesis, therefore, it can be used. . .

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies,. . .

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies,. . .

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies,. . .

DETD . . . the cell surface. The aggregation of FcR having immunoreceptor tyrosine-based activation motifs (ITAMs) activates sequentially src family tyrosine kinases and **syk** family tyrosine kinases that connect transduced signals to common activation pathways shared with other receptors. FcR with ITAMs elicit cell. . . ITAM as signal transduction subunits. The coaggregation of antigen receptors or of FcR

having ITAMs with FcR having immunoreceptor tyrosine-based **inhibition** motifs (ITIMs) negatively regulates cell activation. FcR therefore appear as the subunits of multichain receptors whose constitution is not predetermined. . .

DETD . . . gene or gene product may also useful in the treatment and/or detection of pulmonary defects such as pulmonary edema and **embolism**, bronchitis and cystic fibrosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue. . .

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Polynucleotides and polypeptides of the invention are also useful for the treatment, detection, and/or. . .

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies,. . .

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies,. . .

DETD . . . No. WO 97/34911), Fas Ligand (Takahashi et al., Int. Immunol., 6:1567-1574 (1994)), VEGI (See, International Publication No. WO 99/23105), a **thrombotic** agent or an anti-angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"),. . .

DETD . . . limited to, acidic and basic fibroblast growth factors, VEGF-1, VEGF-2 (VEGF-C), VEGF-3 (VEGF-B), epidermal growth factor alpha and beta, platelet-derived **endothelial** cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin like growth factor, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and **nitric oxide synthase**.

DETD . . . or antagonists of the present invention could also be used to modulate hemostatic (the stopping of bleeding) or thrombolytic activity (**clot** formation). For example, by increasing hemostatic or thrombolytic activity, a polynucleotides or polypeptides, or agonists or antagonists of the present. . .

DETD Myocardial ischemias include coronary disease, such as angina pectoris, coronary aneurysm, coronary arteriosclerosis, coronary **thrombosis**, coronary vasospasm, myocardial infarction and myocardial stunning.

DETD . . . Arteritis, aortitis, Leriche's Syndrome, arterial occlusive diseases, arteritis, enarteritis, polyarteritis nodosa, cerebrovascular diseases, disorders, and/or conditions, diabetic angiopathies, diabetic retinopathy, **embolisms**, **thrombosis**, erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension, ischemia, peripheral vascular diseases, phlebitis, pulmonary veno-occlusive disease, Raynaud's disease, CREST syndrome, retinal. . .

DETD . . . include carotid artery diseases, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformation, cerebral artery diseases, cerebral

embolism and **thrombosis**, carotid artery **thrombosis**, sinus **thrombosis**, Wallenberg's syndrome, cerebral hemorrhage, epidural hematoma, subdural hematoma, subaraxhnoid hemorrhage, cerebral infarction, cerebral ischemia (including transient), subclavian steal syndrome, periventricular. . .

DETD **Embolisms** include air **embolisms**, amniotic fluid **embolisms**, cholesterol **embolisms**, blue toe syndrome, fat **embolisms**, pulmonary **embolisms**, and thromoboembolisms. **Thrombosis** include coronary **thrombosis**, hepatic vein **thrombosis**, retinal vein occlusion, carotid artery **thrombosis**, sinus **thrombosis**, Wallenberg's syndrome, and thrombophlebitis.

DETD . . . cell growth, may be employed in treatment for stimulating re-vascularization of ischemic tissues due to various disease conditions such as **thrombosis**, arteriosclerosis, and other cardiovascular conditions. These polypeptide may also be employed to stimulate angiogenesis and limb regeneration, as discussed above.

INCL INCLM: 530/350.000
INCLS: 435/069.100; 435/320.100; 435/325.000; 536/023.500

NCL NCLM: 530/350.000
NCLS: 435/069.100; 435/320.100; 435/325.000; 536/023.500

IC IPCI C07K0014-47 [I,A]; C07K0014-435 [I,C*]; C07H0021-04 [I,A]; C07H0021-00 [I,C*]; C12P0021-06 [I,A]
IPCR C07K0014-435 [I,C]; C07K0014-47 [I,A]; C07H0021-00 [I,C]; C07H0021-04 [I,A]; C12P0021-06 [I,C]; C12P0021-06 [I,A]

			PATENT	KIND	DATE
OS	CA 129:132225	* WO	9831800	A2	19980723
	CA 141:135218	EP	1439189	A2	20040721
	CA 136:1102	US	6326392	B1	20011204
	CA 136:130548	US	6342581	B1	20020129
	CA 137:58593	US	6410709	B1	20020625
	CA 137:164736	US	6433139	B1	20020813
	CA 137:212635	US	6444440	B1	20020903
	CA 137:228383	US	6448230	B1	20020910
	CA 137:347552	US	6475753	B1	20021105
	CA 137:347556	US	6476195	B1	20021105
	CA 138:3688	US	6486301	B1	20021126
	CA 138:199986	US	6525174	B1	20030225
	CA 138:249901	US	6534631	B1	20030318
	CA 139:2104	US	6569992	B1	20030527
	CA 139:174865	US	6605699	B1	20030812
	CA 145:204086	US	7091315	B1	20060815
	CA 136:211966	US	20020028449	A1	20020307
	CA 136:320406	US	20020045230	A1	20020418
	CA 137:29063	US	20020068319	A1	20020606
	CA 137:42653	US	20020076756	A1	20020620
	CA 137:42654	US	20020077287	A1	20020620
	CA 137:136076	US	20020106780	A1	20020808
	CA 137:196765	US	20020120103	A1	20020829
	CA 137:305805	US	20020151009	A1	20021017
	CA 137:348416	US	20020160493	A1	20021031
	CA 137:347570	US	20020165137	A1	20021107
	CA 138:1115	US	20020172994	A1	20021121
	CA 138:38085	US	20020193305	A1	20021219
	CA 138:50938	US	20020198143	A1	20021226
	CA 138:78434	US	20030008813	A1	20030109

CA 138:148748	US	20030027297	A1	20030206
CA 138:148752	US	20030028003	A1	20030206
CA 140:194487	US	20030049618	A1	20030313
CA 138:233059	US	20030050455	A1	20030313
CA 138:249928	US	20030054443	A1	20030320
CA 138:397343	US	20030100051	A1	20030529
CA 139:192525	US	20030157508	A1	20030821
CA 139:208874	US	20030166541	A1	20030904
CA 139:272072	US	20030181692	A1	20030925
CA 140:13734	US	20030225009	A1	20031204
CA 140:72162	US	20040002591	A1	20040101
CA 140:88751	US	20040005579	A1	20040108
CA 140:88775	US	20040009491	A1	20040115
CA 140:88779	US	20040010132	A1	20040115
CA 140:158660	US	20040034196	A1	20040219
CA 140:212072	US	20040044191	A1	20040304
CA 143:261424	US	20050197285	A1	20050908
CA 143:300330	US	20050208602	A1	20050922
CA 143:300338	US	20050214786	A1	20050929
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* CA Indexing for this record included
CC    3-3 (Biochemical Genetics)
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ST    human protein cDNA sequence
IT    Proteins, specific or class
        (ADF (adipocyte differentiation factor); cloning and cDNA sequences of
        human proteins)
IT    Proteins, specific or class
        (AIF-2 (allograft inflammatory factor-2); cloning and cDNA sequences of
        human proteins)
IT    Proteins, specific or class
        (AIF-3 (allograft inflammatory factor-3); cloning and cDNA sequences of
        human proteins)
IT    Proteins, specific or class
        (BEF (brain-enriched hyaluronan-binding factor); cloning and cDNA
        sequences of human proteins)
IT    Proteins, specific or class
        (Bcl-like; cloning and cDNA sequences of human proteins)
IT    Chemokines
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        of human proteins)
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IT    Cytokines
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        human proteins)
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(nucleotide sequence; cloning and cDNA sequences of human proteins)

L11 ANSWER 6 OF 9 USPATFULL on STN
ACCESSION NUMBER: 2006:86473 USPATFULL
TITLE: Methods and compositions for detecting the activation state of multiple proteins in single cells
INVENTOR(S): Perez, Omar D., Stanford, CA, UNITED STATES
Nolan, Garry P., San Francisco, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20060073474	A1	20060406
APPLICATION INFO.:	US 2002-193462	A1	20020710 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-304434P	20010710 (60)
	US 2001-310141P	20010802 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: DORSEY & WHITNEY LLP, Suite 3400, Four Embarcadero Center, San Francisco, CA, 94111-4187, US
NUMBER OF CLAIMS: 32
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 101 Drawing Page(s)
LINE COUNT: 9021
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
DRWD FIG. 16 depicts the results of experiments demonstrating that ICAM-2/LFA-1 interaction is transmitted to Raf by PYK2 and **SYK**. **Inhibitor** screens using various pharmacological **inhibitors** to Src related kineses identify PYK2 and **SYK** to be necessary in relaying the ICAM-2 induced signal to Raf and p44/42 MAPK kinase. Serum starved cells were treated. . . . standard immunoblot procedures. Control IgG dissolved in 0.1% DMSO served as negative control. Blots are representative of triplicate experiments. B) **SYK** and PYK interaction with LFA-1 subunits is intensified upon ICAM-2 interaction. Co-immunoprecipitation experiments were performed immunoprecipitating αL and β2 integrin and immunoblotting for the presence of **SYK** and PYK as a function of a stimulus for 30 minutes as indicated (antibodies used at 10 μg/ml, compounds used at 1 μM and control 19 served as negative control). Reciprocal co-immunoprecipitations confirm PYK and **SYK** associations with β2 integrin (bottom panel). C) PYK2 is phosphorylated in the presence of ICAM-2 or additional stimuli as determined. . .
DRWD FIG. 36 depicts the results of experiments demonstrating ICAM-2 induced phosphorylation of Pyk2 and **Syk**, and p2 integrin association. A) Phospho-raf and phospho-p44/42 immunoblot **inhibition** profile by tyrosine kinase **inhibitors**. 1+10.sup.6 cells were treated with indicated compound (10 μM, 30 min) and then stimulated with ICAM-2 (10 μg/ml, 30 min). Cell lysates were immunoblotted for phospho-raf and phospho-p44/42. Compound alone did not induce detectable phosphorylation. B) Pyk2 and **Syk** are

phosphorylated and co-immunoprecipitate with β2 integrin upon ICAM-2 stimulus. Phospho-specificity was determined by phospho-PykpY402 and phospho-**syk**(Tyr525/526) antibodies. C) Kinetic analyses of the phosphorylation state of PKCα/β, Pyk2, and **Syk** as a function of ICAM-2 stimulus per time. Cells were treated and processed as above. Phospho-specific PKCα/β.sub.II(Thr638) and the following antibodies were used; Pyk2 and **Syk** were first immunoprecipated, probed with anti-phosphotyrosine antibody (PY20), stripped and subsequently probed with indicated non-phospho specific antibody. Immunoblots are representative. . .

DRWD E) depicts that LFA-1 induced phosphorylation of Pyk2 and **Syk** is dependent on PKC. We screened for the **inhibition** of sICAM-2 induced Pyk2 and **Syk** phosphorylation by chemical **inhibitors** to tyrosine kinases using a phospho-tyrosine based ELISA. Pyk2 phosphorylation was abrogated in the presence of PKC **inhibitors** bisindolymaleimide II (BIM II) and staurosporine (STP), in addition to tyrphostin A9, a specific Pyk2 **inhibitor** . Pyk2 phosphorylation was also affected by **inhibitors** of phospholipase Cg (neomycin), **inhibitors** of **Syk** (piceatannol), and PKC **inhibitor** BIM I (Supplementary FIG. 4A). **Syk** phosphorylation was completely abolished by **inhibition** of Pyk2, PLCg1, and strongly affected by PKC **inhibitors**. Thus, both Pyk2 and **Syk** phosphorylations were dependent on PKC activity, while **Syk** phosphorylation was additionally dependent on PLCg1 and Pyk2 activity. It was not possible to assess specific PKC isozymes by this. . .

DRWD A chemical genetic approach was undertaken to determine the hierarchy of PKC, Pyk2, PLCg1, and **Syk** activities in response to sICAM-2 stimulus by verifying phosphorylation status of each kinase in the presence of respective chemical **inhibitors**. **Inhibition** of PKC with BIM II abrogated phosphorylation of Pyk2, PLCg1, and **Syk**. **Inhibition** of PLCg1 by neomycin abrogated phosphorylation of **Syk**, with no **inhibition** observed for Pyk2. **Inhibition** of **Syk** by piceatannol did not block phosphorylation of Pyk2 or PLCg1. These observations suggest that PKC activation is upstream of PYK2, PLCg, and **SYK** activities, and also that **SYK** activity is consequential to PYK2 and PLCg1 activity. Thus, the upstream signaling events from LFA-1 to Raf-1 appear to involve PKC/Pyk2/PLCg1/**Syk**. However, we acknowledge that phospho-protein immunoprecipitation techniques do not exclude the possibility of these molecules existing in complexes. We are. . .

DETD . . . on target tissues. Targeting of: leukocytes to distinct cellular environments is of pivotal importance in cellular processes such as blood **clot** formation (Bowes et al., 1995; Nagaoka et al., 2000; Schleef et al., 2001), immune surveillance (Patarroyo and Makgoba, 1989; Plate. . .

DETD . . . of ICAM-2/LFA-1 interaction. ICAM-2/LFA-1 induced p44/42 MAPK activity was dependent on proline-rich tyrosine kinase 2 (PYK2) and spleen tyrosine kinase (**SYK**), members of the Src family non-receptor tyrosine kineses, and p44/42 activity was abrogated with specific pharmacological **inhibitors** piceatannol and tyrphostin A9 respectively. Confocal microscopy reveals that there is a re-distribution of both PYK2 and **SYK** to the cellular membrane upon LFA-1 engagement with ICAM-2 and that this interaction yields phosphorylation of PYK2. Furthermore, PYK2 and **SYK** co immunoprecipated with LFA-1 only after engagement of ICAM-2, indicating a ligand induced conformational change was responsible for the interaction.

DETD . . . that would be responsible for signal transmission from LFA-1 to Raf (and subsequently to p44/42 MAPK), a series of kinase

inhibitor screens were conducted. Tyrphostin A9 and piceatannol, specific **inhibitors** of proline-tyrosine kinase 2 (PYK2) and Spleen-tyrosine kinase (**SYK**) respectively (Avdi et al., 2001; Fuortes et al., 1999) were found to abrogate the ICAM-2 induced activation of Raf and. . . the src related tyrosine kineses p56Lck and Src were not found to be involved by the inability of specific pharmacological **inhibitors** of these kineses to block ICAM-2 induced p44/42 MAPK activity. Furthermore, immunoblotting for phosphotyrosine residues of immunoprecipitated tyrosine kineses involved. . .

DETD **SYK** is a spleen non-receptor tyrosine kinase that is essential in signal transmission of αIIIβ3 inside out signaling (Saci et al.,. . . by integrin mediated signaling (Miller et al., 1999; Moores et al., 2000). Given the numerous reports depicting both PYK2 and **SYK** phosphorylation events, these events can be categorized by stimulatory conditions and present differential outcomes among different cell types: (1) signaling. . . the ICAM-2/LFA-1 induced signal to Raf, the upstream kinase in the RAF/MEK/ERK cascade, as determined by usage of specific pharmacological **inhibitors** piceatannol and tryphostin A9 in Jurkat T cells. PYK2 and **SYK** interactions have been reported in G protein coupled MAPK activity in PC12 cells (Dikic et al., 1996) and activation of HL40 cells (Miura et al., 2000), supporting the notion of PYK2 and **SYK** interactions in cellular processes.

DETD . . . a number of downstream effectors contribute to cell survival that include, apart from those investigated here, human caspase 9, and **eNOS** (endothelial cells) which promotes angiogenesis of vascular endothelium (Cardone et al., 1998; Kureishi et al., 2000) AKT hyperactivity has been. . .

DETD . . . (Graff et al., 2000). In addition, AKT has the ability to phosphorylate and inactivate caspase 9 (human caspase 9), phosphorylate **eNOS** (endothelial cells) and promote angiogenesis of vascular endothelium, and potentially other substrates (Cardone et al., 1998; Kureishi et al., 2000).. . .

DETD The present inventors undertook flow cytometric based p44/42 MAPK kinase **inhibition** and activation profiling to identify necessary components for LFA-1 signaling. PKC **inhibitor** BIM I, cytoskeletal disrupting agents cytochalisin D, taxol, nocodozole, and sequestering of divalent cations by EDTA diminished the ICAM-2 induced. . . cytoskeleton. To identify upstream kinases that were responsible for signal transmission from LFA-1 to p44/42 MAPK, a series of kinase **inhibitors** were applied and tested for their ability to abrogate the ICAM-2 induced p44/42 MAPK activity (FIG. 34H-I), whereas Herbimycin A and Emodin, **inhibitors** of src and p56lck had no effect. Tyrphostin A9 and piceatannol, specific **inhibitors** of proline-tyrosine kinase 2 (Pyk2) and Spleen-tyrosine kinase (**Syk**), respectively (Avdi et al., 2001; Fuortes et al., 1999) abrogated the ICAM-2 induced activation of p44/42 MAPK and its upstream. . .

DETD We focused on the CD56.sup.+CD8.sup.+ cells (both the CD8.sup.med and CD8.sup.high subsets) and tested if **inhibition** of **Syk** , p44/42 MAPK or disruption of the cytoskeleton detrimentally affected effector-target (E:T) cell conjugation as measured by a flow cytometric conjugate. . . and microtubules enhanced E:T conjugate formation (FIG. 39A) congruent with prior results that disruption by these agents enhanced LFA-1 activation. **Inhibition** of **Syk** by piceatannol **inhibited** conjugate formation whereas **inhibiting** p44/42 MAPK by PD98059 did not (FIG. 39A). These results suggest that **Syk** activity is necessary for LFA-1 adhesion of effector-target cells and is consistent with a report indicating that **Syk**/ZAP-70 are necessary for LFA-1 to LFA-1

activation on the same cell (Soede et al., 1999). p44/42 MAPK appeared to not. . .

DETD Several chemical **inhibition** screens were designed to identify the proteins involved in the LFA-1 to p44/42 MAPK signaling event. Both Pyk2 and **Syk** were identified to be necessary for activation of the p44/42 MAPK pathway and were dependent on PKC activity upon ICAM-2. . . shown to be necessary for p44/42 MAPK activity in other model systems (Barsacchi et al., 1999; Lev et al., 1995). **Syk** is a tyrosine kinase essential in αIIIβ3 signaling (SacI et al., 2000), and links FcεRI signaling to the ras/MAPK pathway (Jabril-Cuenod et al., 1996). **Inhibition** or ablation of **Syk**, either by pharmacological means (via **inhibition** by piceatannol), biochemical means (dominant negative **Syk**), or genetic means (**Syk**.sup.-/- mice) **inhibits** natural cytotoxicity (Brumbaugh et al., 1997; Colucci et al., 1999). Thus LFA-1 activation signaling to **Syk**, a kinase that has been shown to be important for NK cell function, provides a biochemical link between surface integrin. . .

DETD The present inventors demonstrated that both Pyk2 and **Syk** are necessary in ICAM-2 induced LFA-1 signaling to Raf-1, the upstream kinase in the p44/42 MAPK (RAF/MEK/ERK) cascade. **Inhibition** of p44/42 MAPK did not prevent the occurrence of CD56.sup.+CD8.sup.+ cell conjugation. By immunofluorescence analysis, it has been shown that treatment of the NK leukemic cell line YT with the p44/42 MAPK **inhibitor** PD98059 **inhibits** perforin redistribution to the site of effector-target cell contact (Wei et al., 1998). In addition, the p44/42 MAPK pathway has. . .

INCL INCLM: 435/006.000
NCL NCLM: 435/006.000
IC IPCI C12Q0001-68 [I,A]
IPCR C12Q0001-68 [I,A]; C12Q0001-48 [I,C*]; C12Q0001-48 [I,A]; C12Q0001-68 [I,C]; G01N0033-50 [I,C*]; G01N0033-50 [I,A]; G01N0033-569 [I,C*]; G01N0033-569 [I,A]; G01N0033-573 [I,C*]; G01N0033-573 [I,A]

CHEMICAL ABSTRACTS INDEXING COPYRIGHT 2009 ACS on STN

			PATENT	KIND	DATE
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	CA 141:3821	US	20040106156	A1	20040603
	CA 142:459766	US	20050112700	A1	20050526

* CA Indexing for this record included

CC 9-10 (Biochemical Methods)
Section cross-reference(s): 7, 13, 15

ST protein kinase activation phosphorylation immunodetection single cell; phosphatidylinositol kinase activation phosphorylation immunodetection; ICAM2 signaling activation phosphorylation immunodetection

IT CD antigens
(CD102; phosphorylation-specific kinase antibodies and methods for simultaneously detecting the activation state of multiple proteins in single cells)

IT CD antigens
(CD18, association of; phosphorylation-specific kinase antibodies and methods for simultaneously detecting the activation state of multiple proteins in single cells)

IT CD antigens
(CD50; phosphorylation-specific kinase antibodies and methods for simultaneously detecting the activation state of multiple proteins in single cells)

IT Cytometry
(FACS (fluorescence-activated cell sorting); phosphorylation-specific kinase antibodies and methods for simultaneously detecting the activation state of multiple proteins in single cells)
IT Cell adhesion molecules
(ICAM-2 (intercellular adhesion mol. 2); phosphorylation-specific kinase antibodies and methods for simultaneously detecting the activation state of multiple proteins in single cells)
IT Cell adhesion molecules
(ICAM-3 (intercellular adhesion mol. 3); phosphorylation-specific kinase antibodies and methods for simultaneously detecting the activation state of multiple proteins in single cells)
IT Cell adhesion molecules
(Leu-CAM (leukocytic cell adhesion mol.), association of; phosphorylation-specific kinase antibodies and methods for simultaneously detecting the activation state of multiple proteins in single cells)
IT Cell activation
(T cell; phosphorylation-specific kinase antibodies and methods for simultaneously detecting the activation state of multiple proteins in single cells)
IT T cell (lymphocyte)
(activation; phosphorylation-specific kinase antibodies and methods for simultaneously detecting the activation state of multiple proteins in single cells)
IT Phosphatidylinositol 3,4,5-trisphosphate
Phosphatidylinositol 4,5-bisphosphate
(antibodies specific for; phosphorylation-specific kinase antibodies and methods for simultaneously detecting the activation state of multiple proteins in single cells)
IT Cytometry
(flow; phosphorylation-specific kinase antibodies and methods for simultaneously detecting the activation state of multiple proteins in single cells)
IT Animal cell
(mammalian; phosphorylation-specific kinase antibodies and methods for simultaneously detecting the activation state of multiple proteins in single cells)
IT Drug screening
Fluorescence resonance energy transfer
Fluorescent indicators
Human
Signal transduction, biological
(phosphorylation-specific kinase antibodies and methods for simultaneously detecting the activation state of multiple proteins in single cells)
IT Proteins
(phosphorylation-specific kinase antibodies and methods for simultaneously detecting the activation state of multiple proteins in single cells)
IT Antibodies and Immunoglobulins
(phosphorylation-specific kinase antibodies and methods for simultaneously detecting the activation state of multiple proteins in single cells)
IT Integrins
LFA-1 (antigen)
(phosphorylation-specific kinase antibodies and methods for simultaneously detecting the activation state of multiple proteins in single cells)
IT CD28 (antigen)

CD3 (antigen)
(signaling; phosphorylation-specific kinase antibodies and methods for simultaneously detecting the activation state of multiple proteins in single cells)
IT 407-41-0 1114-81-4 21820-51-9, Phosphotyrosine
(antibodies specific for; phosphorylation-specific kinase antibodies and methods for simultaneously detecting the activation state of multiple proteins in single cells)
IT 138674-26-7, Protein kinase SYK 170780-46-8, Protein tyrosine kinase PYK2
(phosphorylation of; phosphorylation-specific kinase antibodies and methods for simultaneously detecting the activation state of multiple proteins in single cells)
IT 9031-44-1, Kinase 115926-52-8, Phosphatidylinositol 3-kinase 137632-07-6, p44 Mitogen-activated protein kinase 148640-14-6, Protein kinase AKT 153190-61-5, Protein kinase TYK2 155215-87-5, Protein kinase JNK 165245-96-5, p38 Mitogen-activated protein kinase 186322-81-6, Caspase 216503-95-6, Pro-Caspase
(phosphorylation-specific kinase antibodies and methods for simultaneously detecting the activation state of multiple proteins in single cells)

L11 ANSWER 7 OF 9 USPATFULL on STN
ACCESSION NUMBER: 2005:44214 USPATFULL
TITLE: Methods and compositions for treating cardiovascular disease using 1722, 10280, 59917, 85553, 10653, 9235, 21668, 17794, 2210, 6169, 10102, 21061, 17662, 1468, 12282, 6350, 9035, 1820, 23652, 7301, 8925, 8701, 3533, 9462, 9123, 12788, 17729, 65552, 1261, 21476, 33770, 9380, 2569654, 33556, 53656, 44143, 32612, 10671, 261, 44570, 41922, 2552, 2417, 19319, 43969, 8921, 8993, 955, 32345, 966, 1920, 17318, 1510, 14180, 26005, 554, 16408, 42028, 112091, 13886, 13942, 1673, 54946 or 2419
INVENTOR(S): Stagliano, Nancy E., North Reading, MA, UNITED STATES
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PATENT ASSIGNEE(S): Millennium Pharmaceuticals, Inc. (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20050037946	A1	20050217
APPLICATION INFO.:	US 2004-753267	A1	20040108 (10)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2003-439683P	20030113 (60)
	US 2003-445216P	20030205 (60)
	US 2003-448036P	20030218 (60)
	US 2003-454189P	20030312 (60)
	US 2003-457541P	20030325 (60)
	US 2003-466411P	20030429 (60)
	US 2003-469041P	20030508 (60)
	US 2003-477414P	20030610 (60)
	US 2003-478560P	20030613 (60)
	US 2003-489772P	20030724 (60)
	US 2003-490660P	20030728 (60)

	US 2003-499838P	20030903 (60)
	US 2003-504786P	20030922 (60)
	US 2003-505570P	20030924 (60)
	US 2003-512418P	20031017 (60)
	US 2003-514660P	20031027 (60)
DOCUMENT TYPE:	Utility	
FILE SEGMENT:	APPLICATION	
LEGAL REPRESENTATIVE:	MILLENNIUM PHARMACEUTICALS, INC., 40 Landsdowne Street, CAMBRIDGE, MA, 02139	
NUMBER OF CLAIMS:	20	
EXEMPLARY CLAIM:	1	
LINE COUNT:	9321	

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB . . . for the diagnosis and treatment of cardiovascular disease, including, but not limited to, atherosclerosis, reperfusion injury, hypertension, restenosis, arterial inflammation, **thrombosis** and endothelial cell disorders. Specifically, the present invention identifies the differential expression of 1722, 10280, 59917, 85553, 10653, 9235, 21668,. . .

DETD [0007] A cardiovascular disease can also include **thrombosis**. **Thrombosis** can result from platelet dysfunction, e.g. seen in myocardial infarction, angina, hypertension, lipid disorders, diabetes mellitus; myelodysplastic syndromes; myeloproliferative syndromes (including polycythemia vera and thombocythemia); **thrombotic** thrombocytopenic purpuras; HIV-induced platelet disorders (AIDS-Thrombocytopenia); heparin induced thrombocytopenia; mural cell alterations/interactions leading to platelet aggregation/degranulation, vascular endothelial cell activation/injury,. . .

DETD . . . be used to modulate (e.g., inhibit, treat, or prevent) or diagnose cardiovascular disease, including, but not limited to, atherosclerosis and **thrombosis**.

DETD . . . of a differentially expressed gene may be used as part of a prognostic or diagnostic cardiovascular disease, e.g., artherosclerosis and/or **thrombosis**, evaluation, or may be used in methods for identifying compounds useful for the treatment of cardiovascular disease, e.g., atherosclerosis and/or **thrombosis**. In addition, a differentially expressed gene involved in cardiovascular disease may represent a target gene such that modulation of the. . . will act to cure, heal, alleviate, relieve, alter, remedy, ameliorate, improve or affect a cardiovascular disease condition, e.g., atherosclerosis and/or **thrombosis**. Compounds that modulate target gene expression or activity of the target gene product can be used in the treatment of. . .

DETD . . . role, modulators of 10280 activity would be useful in treating disorders associated with cardiovascular disease, including but not limited to **thrombosis** and atherosclerosis. 10280 polypeptides of the present invention are useful in screening for modulators of 10280 activity.

DETD . . . role, modulators of 59917 activity would be useful in treating disorders associated with cardiovascular disease including but not limited to **thrombosis** and atherosclerosis. 59917 polypeptides of the present invention are useful in screening for modulators of 59917 activity.

DETD . . . role, modulators of 85553 activity would be useful in treating disorders associated with cardiovascular disease including but not limited to **thrombosis** and atherosclerosis. 85553 polypeptides of the present invention are useful in screening for modulators of 85553 activity.

DETD . . . product. The high levels of 1820 mRNA found in megakaryocytes and platelets indicate that 1820, a soluble granule protein, regulates

clot formation following platelet degranulation. Therefore, inhibition of 1820 would provide a means to regulate platelet-rich thrombus formation Due to 1820. . . role, modulators of 1820 activity would be useful in treating disorders associated with cardiovascular disease, including but not limited to **thrombosis**. 1820 polypeptides of the present invention are useful in screening for modulators of 1820 activity.

DETD . . . role, modulators of 23652 activity would be useful in treating disorders associated with cardiovascular disease, including but not limited to **thrombosis**. 23652 polypeptides of the present invention are useful in screening for modulators of 23652 activity.

DETD . . . platelets obtained from patients diagnosed with coronary artery disease. The findings herein support the conclusion that 2417 is involved in **thrombosis**. Furthermore, the recent discovery that P2Y9 activates adenylyl cyclase supports the findings herein that 2417 is involved in **thrombosis**. Thus, 2417 polypeptides of the present invention are useful in screening for modulators of 2417 and modulators of 2417 would be useful in treating **thrombotic** disorders.

DETD . . . provide a means to inhibit platelet activation and thrombus formation. Thus inhibitors of 955 can be used to treat arterial **thrombosis**. 955 polypeptides of the present invention are useful in screening for modulators of 955 activity.

DETD . . . as artery, vein, heart, and in brain cortex and pituitary gland. Additionally, it is highly expressed in human umbilical vein **endothelial** cells. In rats treated with minoxidil, nifedipine or an angiotensin receptor blocker (antihypertensive agents) for three days, expression of 13886. . . aortas compared to vehicle treated controls ($p<0.001$; ANOVA). In rats treated with guanylate cyclase stimulators or activators or L-NAME (a **nitric oxide synthase** inhibitor) for seven days, expression of 13886 mRNA is also significantly down-regulated in aortas compared to vehicle treated controls ($p<0.005$;. . .

DETD [0274] **Inhibitors** of 1673 will have profound effects on phagocytosis and leukocyte attachment/recruitment. In addition **Syk** plays a role in full activation of both NFkB and ERK pathways in macrophages. Thus, an **inhibitor** of **Syk** is expected to decrease the load of highly activated macrophages at the site of vascular inflammation and reduce plaque burden.. . .

DETD . . . or 2419 substrate. Compounds identified using the assays described herein may be useful for treating cardiovascular diseases, e.g., atherosclerosis and/or **thrombosis**.

DETD . . . protein ligand or substrate can, for example, be used to ameliorate cardiovascular diseases, e.g., atherosclerosis, ischemia/reperfusion, hypertension, restenosis, arterial inflammation, **thrombosis** and endothelial cell disorders. Such compounds may include, but are not limited to peptides, antibodies, or small organic or inorganic. . .

DETD . . . identified via assays such as those described herein may be useful, for example, for ameliorating cardiovascular disease, e.g., atherscleros is and/or **thrombosis**. In instances whereby a cardiovascular disease condition results from an overall lower level of 1722, 10280, 59917, 85553, 10653, 9235,. . .

DETD . . . can be confirmed in vivo, e.g., in an animal such as an animal model for cardiovascular disease, e.g., atherosclerosis and/or **thrombosis**, as described herein.

DETD . . . 16408, 42028, 112091, 13886, 13942, 1673, 54946 or 2419 modulator identified herein) in treating a cardiovascular disease, e.g., atherosclerosis and/or **thrombosis**, in a subject. For example, the effectiveness of a 1722, 10280, 59917, 85553, 10653, 9235, 21668,

17794, 2210, 6169, 10102,. . . 13886, 13942, 1673, 54946 or 2419 gene, and preferably, other genes that have been implicated in, for example, atherosclerosis and/or **thrombosis** can be used as a "read out" or marker of the phenotype of a particular cell, e.g., a vascular endothelial. . .

DETD . . . a human, at risk of (or susceptible to) a cardiovascular disease such as atherosclerosis, ischemia/reperfusion injury, hypertension, restenosis, arterial inflammation, **thrombosis**, and endothelial cell disorders. With regard to both prophylactic and therapeutic methods of treatment, such treatments may be specifically tailored. . .

DETD . . . of calcium influx, cellular migration, or formation of atherosclerotic lesions. Subjects at risk for a cardiovascular disease, e.g., atherosclerosis and/or **thrombosis**, can be identified by, for example, any or a combination of the diagnostic or prognostic assays described herein. Administration of. . .

CLM What is claimed is:
1. A method for identifying a compound capable of treating a cardiovascular disorder or a **thrombotic** disorder, comprising:
a) combining a compound to be tested with a 1722, 10280, 59917, 85553, 10653, 9235, 21668, 17794, 2210,. . . identify a compound which binds to the polypeptide, thereby identifying a compound capable of treating a cardiovascular disorder or a **thrombotic** disorder:.

CLM What is claimed is:
5. The method of claim 1, wherein the disorder is aberrant vascularization, atherosclerosis, **thrombosis**, coronary artery disease, hyperlipidemia, dyslipidemia, high blood pressure and heart failure.

CLM What is claimed is:
7. A method for identifying a compound capable of treating a cardiovascular disorder or a **thrombotic** disorder, comprising:
a) combining a compound to be tested with a host cell expressing a 1722, 10280, 59917, 85553, 10653,. . . identify a compound which binds to the polypeptide, thereby identifying a compound capable of treating a cardiovascular disorder or a **thrombotic** disorder.

CLM What is claimed is:
10. The method of claim 7, wherein the disorder is aberrant vascularization, atherosclerosis, **thrombosis**, coronary artery disease, hyperlipidemia, dyslipidemia, high blood pressure and heart failure.

CLM What is claimed is:
12. A method of identifying a subject having a cardiovascular or **thrombotic** disorder, or at risk for developing a cardiovascular or **thrombotic** disorder comprising: a) contacting a sample obtained from the subject comprising polypeptides with a 1722, 10280, 59917, 85553, 10653, 9235,. . . 554, 16408, 42028, 112091, 13886, 13942, 1673, 54946 or 2419 binding substance, thereby identifying a subject having a cardiovascular or **thrombotic** disorder, or at risk for developing a cardiovascular or **thrombotic** disorder.

CLM What is claimed is:
15. A method for treating a subject having a cardiovascular or **thrombotic** disorder characterized by aberrant 1722, 10280, 59917, 85553, 10653, 9235, 21668, 17794, 2210, 6169, 10102, 21061, 17662, 1468, 12282, 6350,. . . 26005, 554, 16408, 42028, 112091, 13886, 13942, 1673, 54946 or 2419 modulator, thereby treating the

subject having a cardiovascular or **thrombotic** disorder.

CLM What is claimed is:
16. The method of claim 15, wherein the disorder is aberrant vascularization, atherosclerosis, **thrombosis**, coronary artery disease, hyperlipidemia, dyslipidemia, high blood pressure and heart failure.

IT Anticoagulants
IT Antihypertensives
IT Atherosclerosis
IT Biomarkers (biological responses)
IT Cardiovascular agents
IT Cardiovascular system, disease
IT Human
IT Hypertension
IT Hypolipemic agents
IT Immunoassay
IT Protein sequences
IT **Thrombosis**
IT cDNA sequences
(nucleic acids and encoded proteins useful for treating cardiovascular disease)
INCL INCLM: 514/001.000
NCL NCLM: 514/001.000
IC [7]
ICM A61K031-00
IPCI A61K0031-00 [ICM,7]
IPCR C07K0014-435 [I,C*]; C07K0014-47 [I,A]

CHEMICAL ABSTRACTS INDEXING COPYRIGHT 2009 ACS on STN

	PATENT	KIND	DATE
OS CA 141:151002 *	WO 2004063340	A2	20040729
CA 142:42596	WO 2004108626	A1	20041216

* CA Indexing for this record included
CC 1-8 (Pharmacology)
Section cross-reference(s): 3, 14
ST gene expression profile cardiovascular disease diagnosis therapy
IT Transport proteins
(ABCA6 (ATP-binding cassette transporter sub-family A member 6); nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT Chemokine receptors
(CMKLR1 (chemokine-like receptor 1); nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT Transport proteins
(GABA transporter; nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT G protein-coupled receptors
(GPR41; nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT Glutamate receptors
(GluR2 subunit; nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT Opioid receptors
(ORL1 (opioid receptor-like 1); nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT Purinoceptors

(P2Y9; nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT Receptors
(TLR-8 (Toll-like receptor-8); nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT Nuclear receptors
(TR3 (testicular receptor 3); nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT Angiogenesis
(aberrant vascularization; nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT Transport proteins
(amino acid transporter, N; nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT Antiarteriosclerotics
(antiatherosclerotics; nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT Artery, disease
Inflammation
(arteritis; nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT Transport proteins
(choline transporter, sequence homolog; nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT Artery, disease
(coronary; nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT Lipids, biological studies
(dyslipidemia; nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT Blood vessel, disease
(endothelium; nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT Heart, disease
(failure; nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT Lipids, biological studies
(hyperlipidemia; nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT Reperfusion
(injury; nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT Diagnosis
(mol.; nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT Anticoagulants
Antihypertensives
Atherosclerosis
Biomarkers (biological responses)
Cardiovascular agents
Cardiovascular system, disease
Human
Hypertension
Hypolipemic agents
Immunoassay
Protein sequences
Thrombosis
cDNA sequences
(nucleic acids and encoded proteins useful for treating cardiovascular disease)

IT CD38 (antigen)
(nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT Antibodies and Immunoglobulins
Antisense nucleic acids
Peptides, biological studies
(nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT Transport proteins
(organic anion transporter OATP8; nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT Transport proteins
(peptide/histidine transporter 1; nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT Transport proteins
(peptide/histidine transporter 2; nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT Injury
(reperfusion; nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT Artery, disease
(restenosis; nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT Genetic methods
(two-hybrid screening; nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT Endothelium
(vascular, disease; nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT 9026-48-6, Pantothenate kinase
(1; nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT 9028-86-8, Aldehyde dehydrogenase
(8; nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT 9026-43-1, Serine protein kinase
(Duet; nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT 37250-10-5, Alcohol dehydrogenase (NAD(P))
(Fe1; nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT 727756-14-1, Reductase, sterol, 1 (human) 727757-08-6 727757-11-1
727757-13-3 727757-15-5 727757-17-7, Dehydratase, carbonate (human)
727757-19-9, Transketolase (human) 727757-21-3 727757-23-5
727757-25-7 727757-27-9 727757-29-1, Oxidase, methylsterol (human)
727757-31-5, Phosphatase, inositol 1- (human) 727757-33-7 727757-35-9
727757-37-1 727757-39-3 727757-41-7, Carboxypeptidase M (human)
727757-43-9, CD38 (antigen) (human) 727757-45-1, Chymase (human)
727757-47-3, N-Acetyltransferase-6 (human) 727757-49-5,
Adenosyltransferase, methionine (human) 727757-51-9, Oxidase, aldehyde (human) 727757-53-1 727757-55-3, Proteinase, gene reelin (human)
727757-57-5, Hydratase, epoxide (human) 727757-59-7 727757-61-1
727757-64-4, Proteinase, metallo-, ADAMTS-15 (human) 727757-66-6,
Orphan receptor HMR (human) 727757-68-8 727757-70-2 727757-72-4,
Oxygenase, homogentisate 1,2-di- (human) 727757-74-6 727757-76-8,
Peptide/histidine transporter 2 (human) 727757-78-0 727757-80-4
727757-82-6, Peptide/histidine transporter 1 (human) 727757-84-8,
Oxygenase, tryptophan 5-mono- (human) 727757-86-0 727757-88-2
727757-90-6, Hydrolase, γ-glutamyl (human) 727757-92-8,
Aminopeptidase, aspartate (human) 727757-94-0, Purinoceptor P2Y9

(human) 727757-96-2 727757-98-4, Oxidase, L-2-hydroxy acid (human) 727758-00-1 727758-02-3 727758-04-5 727758-06-7 727758-08-9 727758-10-3, Glutamate receptor (human GluR2 subunit) 727758-12-5, G protein-coupled receptor GPR41 (human) 727758-14-7 727758-16-9 727758-18-1, Deaminase, adenosine (human) 727758-20-5, GABA transporter (human) 727758-22-7, Methyltransferase, glycine (human) 727758-24-9, Dehydrogenase, sarcosine (human) 727758-26-1 727758-28-3 727758-30-7 727758-32-9 727758-34-1, Chemokine receptor-like 1 (human) 727758-36-3
(amino acid sequence; nucleic acids and encoded proteins useful for treating cardiovascular disease)

IT 69403-07-2, Δ14-Sterol reductase
(isoform 1; nucleic acids and encoded proteins useful for treating cardiovascular disease)

IT 9074-01-5, Pyruvate dehydrogenase kinase
(isoform 3; nucleic acids and encoded proteins useful for treating cardiovascular disease)

IT 9027-33-2, N-Acetyltransferase
(isoform NAT6; nucleic acids and encoded proteins useful for treating cardiovascular disease)

IT 158886-18-1, CAM kinase kinase
(isoform β1; nucleic acids and encoded proteins useful for treating cardiovascular disease)

IT 9001-03-0, Carbonic anhydrase 9012-52-6, Adenosylmethionine synthetase 9014-48-6, Transketolase 9015-81-0, 17β-Hydroxysteroid dehydrogenase 9026-93-1, Adenosine deaminase 9028-71-1, Glycolate oxidase 9029-07-6, Aldehyde oxidase 9029-49-6, Homogentisate 1,2-dioxygenase 9029-78-1, Betaine-homocysteine methyltransferase 9030-45-9, Glucosamine:fructose-6-phosphate aminotransferase 9036-20-8, Adenosylmethionine decarboxylase 9037-21-2, Tryptophan 5-monooxygenase 9048-63-9, Epoxide hydrolase 9074-83-3, Glutamyl aminopeptidase 9074-87-7, Glutamate carboxypeptidase 37184-63-7, Myoinositol-1-monophosphatase 37228-65-2, Sarcosine dehydrogenase 37228-72-1, Glycine methyltransferase 42616-26-2, 4-Methyl sterol oxidase 56093-23-3 63551-76-8, Phospholipase C β4 97501-92-3, Chymase 98668-52-1, ADP-ribosylarginine hydrolase 105638-50-4, L-Isoaspartyl methyltransferase 120038-28-0, Carboxypeptidase M 138674-26-7, Protein kinase SYK 145539-86-2, Hematopoietic cellular kinase 150316-07-7, Mitogen-activated protein kinase kinase kinase 8 161384-20-9, Protein kinase D 188364-80-9, Matrix metalloproteinase 19 190606-17-8, MAP/microtubule affinity-regulating kinase 1 196717-98-3, PTP-PEST 203810-05-3, Protein kinase MRCKβ 205265-41-4, Akt3 kinase 300858-62-2, RPTP-ε 334478-40-9, Protein kinase TRP-PLIK 402736-19-0, Protein kinase Sgk2 404843-77-2, Reelin 677314-64-6, Metalloproteinase ADAMTS-15
(nucleic acids and encoded proteins useful for treating cardiovascular disease)

IT 727757-09-7 727757-10-0 727757-12-2 727757-14-4 727757-16-6 727757-18-8 727757-20-2 727757-22-4 727757-24-6 727757-26-8 727757-28-0 727757-30-4 727757-32-6 727757-34-8 727757-36-0 727757-38-2 727757-40-6 727757-42-8 727757-44-0, DNA (human chymase cDNA plus flanks) 727757-46-2 727757-48-4 727757-50-8 727757-52-0 727757-54-2 727757-56-4 727757-58-6 727757-60-0 727757-62-2 727757-63-3 727757-65-5 727757-67-7 727757-69-9 727757-71-3 727757-73-5 727757-75-7 727757-77-9 727757-79-1 727757-81-5 727757-83-7 727757-85-9 727757-87-1 727757-89-3 727757-91-7 727757-93-9 727757-95-1 727757-97-3 727757-99-5 727758-01-2 727758-03-4 727758-05-6 727758-07-8 727758-09-0 727758-11-4 727758-13-6 727758-15-8 727758-17-0 727758-19-2 727758-21-6 727758-23-8 727758-25-0 727758-27-2 727758-29-4 727758-31-8

727758-33-0 727758-35-2
(nucleotide sequence; nucleic acids and encoded proteins useful for treating cardiovascular disease)
IT 9031-98-5, Carboxypeptidase
(vitellogenic; nucleic acids and encoded proteins useful for treating cardiovascular disease)

L11 ANSWER 8 OF 9 USPATFULL on STN
ACCESSION NUMBER: 2004:45202 USPATFULL
TITLE: 98 human secreted proteins
INVENTOR(S): Komatsoulis, George A., Silver Spring, MD, UNITED STATES
Rosen, Craig A., Laytonsville, MD, UNITED STATES
Ruben, Steven M., Brookeville, MD, UNITED STATES
Duan, D. Roxanne, Bethesda, MD, UNITED STATES
Moore, Paul A., Germantown, MD, UNITED STATES
Shi, Yanggu, Gaithersburg, MD, UNITED STATES
LaFleur, David W., Washington, DC, UNITED STATES
Wei, Ying-Fei, Berkeley, CA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 20040034196	A1	20040219
APPLICATION INFO.:	US 2003-351334	A1	20030127 (10)

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 2000-489847, filed on 24 Jan 2000, GRANTED, Pat. No. US 6476195
Continuation-in-part of Ser. No. WO 1999-US17130, filed on 29 Jul 1999, PENDING

	NUMBER	DATE
PRIORITY INFORMATION:	US 2002-350898P	20020125 (60)
	US 1998-94657P	19980730 (60)
	US 1998-95486P	19980805 (60)
	US 1998-96319P	19980812 (60)
	US 1998-95454P	19980806 (60)
	US 1998-95455P	19980806 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: HUMAN GENOME SCIENCES INC, 9410 KEY WEST AVENUE, ROCKVILLE, MD, 20850
NUMBER OF CLAIMS: 24
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 6 Drawing Page(s)
LINE COUNT: 24589
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
SUMM . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, myocardial infarction, myocarditis, ischemia, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis; pulmonary edema and **embolism**, bronchitis and/or cystic fibrosis; Crohn's disease and/or colon cancer. Similarly, the tissue distribution indicates that polynucleotides and polypeptides corresponding to. . .
SUMM . . . and rhabdomyosarcoma), as well as cardiovascular and respiratory or pulmonary disorders such as asthma, pulmonary edema, pneumonia, atherosclerosis, restenosis, stoke, **thrombosis** hypertension, inflammation and wound healing. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for. . .

SUMM . . . prevention and/or diagnosis of cardiovasular and respiratory or pulmonary disorders such as asthma, pulmonary edema, pneumonia, atherosclerosis, restenosis, stoke, angina, **thrombosis**, hypertension, inflammation, and wound healing.

SUMM . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies,. . .

SUMM . . . of vascular conditions, which include, but are not limited to, microvascular disease, vascular leak syndrome, aneurysm, stroke, atherosclerosis, arteriosclerosis, or **embolism**. For example, this gene product may represent a soluble factor produced by smooth muscle that regulates the innervation of organs. . .

SUMM . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies,. . .

SUMM . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis.

SUMM . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. The gene product may also be involved in lymphopoiesis, therefore, it can be used. . .

SUMM . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies,. . .

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SUMM . . . the cell surface. The aggregation of FcR having immunoreceptor tyrosine-based activation motifs (ITAMs) activates sequentially src family tyrosine kinases and **syk** family tyrosine kinases that connect transduced signals to common activation pathways shared with other receptors. FcR with ITAMs elicit cell. . . ITAM as signal transduction subunits. The coaggregation of antigen receptors or of FcR having ITAMs with FcR having immunoreceptor tyrosine-based **inhibition** motifs (ITIMs) negatively regulates cell activation. FcR therefore appear as the subunits of multichain receptors whose constitution is not predetermined. . .

SUMM . . . gene or gene product may also useful in the treatment and/or

detection of pulmonary defects such as pulmonary edema and **embolism**, bronchitis and cystic fibrosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue. . .

SUMM . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Polynucleotides and polypeptides of the invention are also useful for the treatment, detection, and/or. . .

SUMM . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies,. . .

SUMM . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies,. . .

SUMM . . . No. WO 97/34911), Fas Ligand (Takahashi et al., Int. Immunol., 6:1567-1574 (1994)), VEGI (See, International Publication No. WO 99/23105), a **thrombotic** agent or an anti-angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"),. . .

SUMM . . . limited to, acidic and basic fibroblast growth factors, VEGF-1, VEGF-2 (VEGF-C), VEGF-3 (VEGF-B), epidermal growth factor alpha and beta, platelet-derived **endothelial** cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin like growth factor, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and **nitric oxide synthase**.

SUMM . . . and/or agonists or antagonists of the present invention may be used to modulate hemostatic (the stopping of bleeding) or thrombolytic (**clot** dissolving) activity. For example, by increasing hemostatic or thrombolytic activity, polynucleotides or polypeptides, and/or agonists or antagonists of the present. . .

SUMM . . . polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of the present invention may be used to prevent, diagnose, prognose, and/or treat **thrombosis**, arterial **thrombosis** , venous **thrombosis**, thromboembolism, pulmonary **embolism**, atherosclerosis, myocardial infarction, transient ischemic attack, unstable angina. In specific embodiments, the polynucleotides, polypeptides, antibodies, and/or agonists or antagonists of. . . the present invention may be used for the prevention of occulsion of saphenous grafts, for reducing the risk of periprocedural **thrombosis** as might accompany angioplasty procedures, for reducing the risk of stroke in patients with atrial fibrillation including nonrheumatic atrial fibrillation, for reducing the risk of **embolism** associated with mechanical heart valves and or mitral valves disease. Other uses for the polynucleotides, polypeptides, antibodies, and/or agonists or. . .

SUMM . . . useful in diagnosing, prognosing, preventing, and/or treating bleeding disorders including, but not limited to, thrombocytopenia (e.g., idiopathic thrombocytopenic purpura, and **thrombotic** thrombocytopenic purpura), Von Willebrand's disease, hereditary platelet disorders (e.g., storage pool disease such as Chediak-Higashi and

Hermansky-Pudlak syndromes, thromboxane A2. . .

SUMM . . . post-streptococcal glomerulonephritis), blood vessel disorders of the kidneys (e.g., kidney infarction, atheroembolic kidney disease, cortical necrosis, malignant nephrosclerosis, renal vein **thrombosis**, renal underperfusion, renal retinopathy, renal ischemia-reperfusion, renal artery **embolism**, and renal artery stenosis), and kidney disorders resulting form urinary tract disease (e.g., pyelonephritis, hydronephrosis, urolithiasis (renal lithiasis, nephrolithiasis), reflux. . .

SUMM [1353] Myocardial ischemias include, but are not limited to, coronary disease, such as angina pectoris, coronary aneurysm, coronary arteriosclerosis, coronary **thrombosis**, coronary vasospasm, myocardial infarction and myocardial stunning.

SUMM . . . aortic diseases, Takayasu's Arteritis, aortitis, Leriche's Syndrome, arterial occlusive diseases, arteritis, enarteritis, polyarteritis nodosa, cerebrovascular disorders, diabetic angiopathies, diabetic retinopathy, **embolisms**, **thrombosis**, erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension, ischemia, peripheral vascular diseases, phlebitis, pulmonary veno-occlusive disease, Raynaud's disease, CREST syndrome, retinal. . .

SUMM . . . to, carotid artery diseases, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformation, cerebral artery diseases, cerebral **embolism** and **thrombosis**, carotid artery **thrombosis**, sinus **thrombosis**, Wallenberg's syndrome, cerebral hemorrhage, epidural hematoma, subdural hematoma, subaraxhnoid hemorrhage, cerebral infarction, cerebral ischemia (including transient), subclavian steal syndrome, periventricular. . .

SUMM [1358] **Embolisms** include, but are not limited to, air **embolisms**, amniotic fluid **embolisms**, cholesterol **embolisms**, blue toe syndrome, fat **embolisms**, pulmonary **embolisms**, and thromoboembolisms. **Thrombosis** include, but are not limited to, coronary **thrombosis**, hepatic vein **thrombosis**, retinal vein occlusion, carotid artery **thrombosis**, sinus **thrombosis**, Wallenberg's syndrome, and thrombophlebitis.

SUMM . . . pulmonary hemosiderosis, sarcoidosis and pulmonary alveolar proteinosis), Acute respiratory distress syndrome (also called, e.g., adult respiratory distress syndrome), edema, pulmonary **embolism**, bronchitis (e.g., viral, bacterial), bronchiectasis, atelectasis, lung abscess (caused by, e.g., Staphylococcus aureus or Legionella pneumophila), and cystic fibrosis.

SUMM . . . diseases, damage, disorders, or injury, associated with cerebrovascular disorders including, but not limited to, carotid artery diseases (e.g., carotid artery **thrombosis**, carotid stenosis, or Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral **embolism** and **thrombosis** (e.g., carotid artery **thrombosis**, sinus **thrombosis**, or Wallenberg's Syndrome), cerebral hemorrhage (e.g., epidural or subdural hematoma, or subarachnoid hemorrhage), cerebral infarction, cerebral ischemia (e.g., transient cerebral. . .

SUMM . . . polypeptides, agonists, and/or antagonists of the present invention include cerebrovascular disorders (such as carotid artery diseases which include carotid artery **thrombosis**, carotid stenosis and Moyamoya Disease), cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformations, cerebral artery diseases, cerebral **embolism** and **thrombosis** such as carotid artery

thrombosis, sinus **thrombosis** and Wallenberg's Syndrome, cerebral hemorrhage such as epidural hematoma, subdural hematoma and subarachnoid hemorrhage, cerebral infarction, cerebral ischemia such as. . .

SUMM . . . (e.g., abnormal heart rate (fetal or maternal), breathing problems, and abnormal fetal position), shoulder dystocia, prolapsed umbilical cord, amniotic fluid **embolism**, and aberrant uterine bleeding.

SUMM [1448] Further, diseases and/or disorders of the postdelivery period, including endometritis, myometritis, parametritis, peritonitis, pelvic thrombophlebitis, pulmonary **embolism**, endotoxemia, pyelonephritis, saphenous thrombophlebitis, mastitis, cystitis, postpartum hemorrhage, and inverted uterus.

SUMM . . . diseases and/or disorders include intrahepatic cholestasis (alagille syndrome, biliary liver cirrhosis), fatty liver (alcoholic fatty liver, reye syndrome), hepatic vein **thrombosis**, hepatolentricular degeneration, hepatomegaly, hepatopulmonary syndrome, hepatorenal syndrome, portal hypertension (esophageal and gastric varices), liver abscess (amebic liver abscess), liver cirrhosis. . .

SUMM . . . cell growth, may be employed in treatment for stimulating re-vascularization of ischemic tissues due to various disease conditions such as **thrombosis**, arteriosclerosis, and other cardiovascular conditions. These polypeptide may also be employed to stimulate angiogenesis and limb regeneration, as discussed above.

DETD . . . are not limited to, acidic and basic fibroblast growth factors, VEGF-1, VEGF-2, VEGF-3, epidermal growth factor alpha and beta, platelet-derived **endothelial** cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin-like growth factor, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and **nitric oxide synthase**.

INCL INCLM: 530/350.000
INCLS: 530/388.100; 536/023.500; 435/006.000; 435/069.100; 435/320.100; 435/325.000

NCL NCLM: 530/350.000
NCLS: 435/006.000; 435/069.100; 435/320.100; 435/325.000; 530/388.100; 536/023.500

IC [7]
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ICS C07H021-04; C12P021-02; C12N005-06; C07K014-47; C07K016-40
IPCI C12Q0001-68 [ICM,7]; C07H0021-04 [ICS,7]; C07H0021-00 [ICS,7,C*]; C12P0021-02 [ICS,7]; C12N0005-06 [ICS,7]; C07K0014-47 [ICS,7]; C07K0014-435 [ICS,7,C*]; C07K0016-40 [ICS,7]
IPCR A61K0038-00 [N,C*]; A61K0038-00 [N,A]; C07K0014-435 [I,C*]; C07K0014-47 [I,A]

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CC 3-3 (Biochemical Genetics)
Section cross-reference(s): 6, 13, 63
ST secretory protein cDNA sequence human
IT High throughput screening
(assays; cloning and cDNA and deduced amino acid sequences of 98 human secreted proteins)
IT Epitopes
Human
Molecular cloning
Protein sequences
cDNA sequences
(cloning and cDNA and deduced amino acid sequences of 98 human secreted proteins)
IT Antibodies and Immunoglobulins
(cloning and cDNA and deduced amino acid sequences of 98 human secreted proteins)
IT Gene, animal
(cloning and cDNA and deduced amino acid sequences of 98 human secreted proteins)
IT Disease, animal
(diagnosis and treatment of; cloning and cDNA and deduced amino acid sequences of 98 human secreted proteins)
IT Animal tissue

(expression profiles; cloning and cDNA and deduced amino acid sequences of 98 human secreted proteins)

IT Genetic mapping
(gene location on human chromosome; cloning and cDNA and deduced amino acid sequences of 98 human secreted proteins)

IT Chromosome
(human, gene location on; cloning and cDNA and deduced amino acid sequences of 98 human secreted proteins)

IT Diagnosis
(mol., by mutation detection or changes in expression; cloning and cDNA and deduced amino acid sequences of 98 human secreted proteins)

IT Proteins
(secretory; cloning and cDNA and deduced amino acid sequences of 98 human secreted proteins)

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(amino acid sequence; cloning and cDNA and deduced amino acid sequences of 98 human secreted proteins)

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(nucleotide sequence; cloning and cDNA and deduced amino acid sequences of 98 human secreted proteins)

IT 655458-69-8 655458-71-2 655458-72-3 655458-73-4 655458-74-5
655458-75-6 655458-76-7 655458-77-8 655458-78-9
(unclaimed nucleotide sequence; cloning and cDNA and deduced amino acid sequences of 98 human secreted proteins)

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655459-68-0
(unclaimed protein sequence; cloning and cDNA and deduced amino acid sequences of 98 human secreted proteins)

L11 ANSWER 9 OF 9 USPATFULL on STN
ACCESSION NUMBER: 2002:291062 USPATFULL
TITLE: Secreted protein HNFGF20
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10537599

PATENT ASSIGNEE(S):	Human Genome Sciences, Inc., Rockville, MD, United States (U.S. corporation)

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PATENT INFORMATION:	US 6476195	B1	20021105
APPLICATION INFO.:	US 2000-489847		20000124 (9)
RELATED APPLN. INFO.:	Continuation-in-part of Ser. No. WO 1999-US17130, filed on 29 Jul 1999		

	NUMBER	DATE
PRIORITY INFORMATION:	US 1998-94657P	19980730 (60)
	US 1998-95486P	19980805 (60)
	US 1998-96319P	19980812 (60)
	US 1998-95454P	19980806 (60)
	US 1998-95455P	19980806 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	GRANTED
PRIMARY EXAMINER:	Jones, W. Gary
ASSISTANT EXAMINER:	Goldberg, Jeanine
LEGAL REPRESENTATIVE:	Human Genome Sciences, Inc.
NUMBER OF CLAIMS:	36
EXEMPLARY CLAIM:	1,7
NUMBER OF DRAWINGS:	3 Drawing Figure(s); 3 Drawing Page(s)
LINE COUNT:	20107

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, myocardial infarction, myocarditis, ischemia, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis; pulmonary edema and **embolism**, bronchitis and/or cystic fibrosis; Crohn's disease and/or colon cancer. Similarly, the tissue distribution indicates that polynucleotides and polypeptides corresponding to. . .

DETD . . . and rhabdomyosarcoma), as well as cardiovascular and respiratory or pulmonary disorders such as asthma, pulmonary edema, pneumonia, atherosclerosis, restenosis, stoke, **thrombosis** hypertension, inflammation and wound healing. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for. . .

DETD . . . prevention and/or diagnosis of cardiovasular and respiratory or pulmonary disorders such as asthma, pulmonary edema, pneumonia, atherosclerosis, restenosis, stoke, angina, **thrombosis**, hypertension, inflammation, and wound healing.

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies,. . .

DETD . . . of vascular conditions, which include, but are not limited to, microvascular disease, vascular leak syndrome, aneurysm, stroke, atherosclerosis, arteriosclerosis, or **embolism**. For example, this gene product may represent a soluble factor produced by smooth muscle that regulates the innervation of organs. . .

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore,

the protein may also be used to determine biological activity, to raise antibodies,. . .

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis.

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. The gene product may also be involved in lymphopoiesis, therefore, it can be used. . .

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies,. . .

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies,. . .

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies,. . .

DETD . . . the cell surface. The aggregation of FcR having immunoreceptor tyrosine-based activation motifs (ITAMs) activates sequentially src family tyrosine kinases and **syk** family tyrosine kinases that connect transduced signals to common activation pathways shared with other receptors. FcR with ITAMs elicit cell. . . ITAM as signal transduction subunits. The coaggregation of antigen receptors or of FcR having ITAMs with FcR having immunoreceptor tyrosine-based **inhibition** motifs (ITIMs) negatively regulates cell activation. FcR therefore appear as the subunits of multichain receptors whose constitution is not predetermined. . .

DETD . . . gene or gene product may also useful in the treatment and/or detection of pulmonary defects such as pulmonary edema and **embolism**, bronchitis and cystic fibrosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue. . .

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Polynucleotides and polypeptides of the invention are also useful for the treatment, detection, and/or. . .

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies,. . .

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary

artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies,. . .

DETD . . . No. WO 97/34911), Fas Ligand (Takahashi et aL, Int. Immunol., 6:1567-1574 (1994)), VEGI (See, International Publication No. WO 99/23105), a **thrombotic** agent or an anti-angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"),. . .

DETD . . . limited to, acidic and basic fibroblast growth factors, VEGF-1, VEGF-2 (VEGF-C), VEGF-3 (VEGF-B), epidermal growth factor alpha and beta, platelet-derived **endothelial** cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin like growth factor, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and **nitric oxide synthase**.

DETD . . . or antagonists of the present invention could also be used to modulate hemostatic (the stopping of bleeding) or thrombolytic activity (**clot** formation). For example, by increasing hemostatic or thrombolytic activity, a polynucleotides or polypeptides, or agonists or antagonists of the present. . .

DETD Myocardial ischemias include coronary disease, such as angina pectoris, coronary aneurysm, coronary arteriosclerosis, coronary **thrombosis**, coronary vasospasm, myocardial infarction and myocardial stunning.

DETD . . . Arteritis, aortitis, Leriche's Syndrome, arterial occlusive diseases, arteritis, enarteritis, polyarteritis nodosa, cerebrovascular diseases, disorders, and/or conditions, diabetic angiopathies, diabetic retinopathy, **embolisms**, **thrombosis**, erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension, ischemia, peripheral vascular diseases, phlebitis, pulmonary veno-occlusive disease, Raynaud's disease, CREST syndrome, retinal. . .

DETD . . . include carotid artery diseases, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformation, cerebral artery diseases, cerebral **embolism** and **thrombosis**, carotid artery **thrombosis**, sinus **thrombosis**, Wallenberg's syndrome, cerebral hemorrhage, epidural hematoma, subdural hematoma, subaraxhnoid hemorrhage, cerebral infarction, cerebral ischemia (including transient), subclavian steal syndrome, periventricular. . .

DETD **Embolisms** include air **embolisms**, amniotic fluid **embolisms**, cholesterol **embolisms**, blue toe syndrome, fat **embolisms**, pulmonary **embolisms**, and thromoboembolisms. **Thrombosis** include coronary **thrombosis**, hepatic vein **thrombosis**, retinal vein occlusion, carotid artery **thrombosis**, sinus **thrombosis**, Wallenberg's syndrome, and thrombophlebitis.

DETD . . . cell growth, may be employed in treatment for stimulating revascularization of ischemic tissues due to various disease conditions such as **thrombosis**, arteriosclerosis, and other cardiovascular conditions. These polypeptide may also be employed to stimulate angiogenesis and limb regeneration, as discussed above.

INCL INCLM: 530/350.000
INCLS: 530/350.000; 435/006.000; 435/007.100; 536/023.100

NCL NCLM: 530/350.000
NCLS: 435/006.000; 435/007.100; 536/023.100

IC [7]
ICM C07K005-00
ICS C07K014-00; C12Q001-68; C07H021-04

IPCI C07K0005-00 [ICM,7]; C07K0014-00 [ICS,7]; C12Q0001-68 [ICS,7];
C07H0021-04 [ICS,7]; C07H0021-00 [ICS,7,C*]
IPCR C07K0014-435 [I,C*]; C07K0014-47 [I,A]
EXF 536/23.1; 435/6; 435/7.1; 530/350; 530/300
ARTU 164

CHEMICAL ABSTRACTS INDEXING COPYRIGHT 2009 ACS on STN

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* CA Indexing for this record included
CC 3-3 (Biochemical Genetics)
Section cross-reference(s): 6, 13, 63
ST secretion protein HNFGF20 cDNA sequence human
IT Bone marrow

10537599

(CD34+ cell of; human secreted protein HNFGF20, its protein and cDNA sequences and therapeutic use thereof)
IT T cell (lymphocyte)
(CD34+, proliferation stimulation by HNFGF20; human secreted protein HNFGF20, its protein and cDNA sequences and therapeutic use thereof)
IT Cell proliferation
(HNFGF20 as the stimulator of; human secreted protein HNFGF20, its protein and cDNA sequences and therapeutic use thereof)
IT Hematopoietic precursor cell
(HNFGF20 as the stimulator to; human secreted protein HNFGF20, its protein and cDNA sequences and therapeutic use thereof)
IT Gene, animal
(cDNA for human secreted protein HNFGF20)
IT Immunity
(disorder; human secreted protein HNFGF20, its protein and cDNA sequences and therapeutic use thereof)
IT cDNA sequences
(for human secreted protein HNFGF20)
IT Drug screening
Gene therapy
Genetic mapping
Genetic vectors
Molecular cloning
Nucleic acid hybridization
(human secreted protein HNFGF20, its protein and cDNA sequences and therapeutic use thereof)
IT Primers (nucleic acid)
Probes (nucleic acid)
(human secreted protein HNFGF20, its protein and cDNA sequences and therapeutic use thereof)
IT Chromosome
(human, chromosomal mapping of secreted protein genes; human secreted protein HNFGF20, its protein and cDNA sequences and therapeutic use thereof)
IT Diagnosis
(mol.; human secreted protein HNFGF20, its protein and cDNA sequences and therapeutic use thereof)
IT Human
Protein sequences
(of human secreted protein HNFGF20)
IT High throughput screening
(of human secreted proteins)
IT Proteins
(secretory, HNFGF20, of human; human secreted protein HNFGF20, its protein and cDNA sequences and therapeutic use thereof)
IT Antibodies and Immunoglobulins
(to human secreted proteins)
IT Bone marrow
(toxicity, CD34+ cell of; human secreted protein HNFGF20, its protein and cDNA sequences and therapeutic use thereof)

=> d his

(FILE 'HOME' ENTERED AT 17:31:59 ON 16 JAN 2009)

FILE 'USPATFULL, USPATOLD, USPAT2' ENTERED AT 17:32:24 ON 16 JAN 2009
L1 2 S ENDOTHELIAL CELL DERIVED NITRIC OXIDE SYNTHASE
L2 2641 S ENDOTHELIAL (S) NITRIC OXIDE SYNTHASE
L3 2407 S ENOS

Jagoe

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L4         4256 S L1 OR L2 OR L3
L5        71645 S THROMBOSIS OR THROMBOTIC OR PLATELET AGGREGATE OR CLOT OR THR
L6         1678 S L4 AND L5
L7          825 S INHIBIT? (S) SYK
L8          243 S INHIBIT? (S) SYK KINASE
L9            3 S L8 AND L6
L10           9 S L7 AND L6
L11           9 DUP REM L10 (0 DUPLICATES REMOVED)

=> s l11 and pd<2003
L12           1 L11 AND PD<2003

=> d l12 ibib

L12  ANSWER 1 OF 1  USPATFULL on STN
ACCESSION NUMBER:       2002:291062  USPATFULL
TITLE:                  Secreted protein HNFGF20
INVENTOR(S):            Komatsoulis, George, Silver Spring, MD, United States
                        Rosen, Craig A., Laytonsville, MD, United States
                        Ruben, Steven M., Olney, MD, United States
                        Duan, Roxanne D., Bethesda, MD, United States
                        Moore, Paul A., Germantown, MD, United States
                        Shi, Yanggu, Gaithersburg, MD, United States
                        LaFleur, David W., Washington, DC, United States
                        Wei, Ying-Fei, Berkeley, CA, United States
                        Ni, Jian, Rockville, MD, United States
                        Florence, Kimberly A., Rockville, MD, United States
                        Young, Paul, Gaithersburg, MD, United States
                        Brewer, Laurie A., St. Paul, MN, United States
                        Soppet, Daniel R., Centreville, VA, United States
                        Endress, Gregory A., Potomac, MD, United States
                        Ebner, Reinhard, Gaithersburg, MD, United States
                        Olsen, Henrik, Gaithersburg, MD, United States
                        Mucenski, Michael, Cincinnati, OH, United States
PATENT ASSIGNEE(S):     Human Genome Sciences, Inc., Rockville, MD, United
                        States (U.S. corporation)

                             NUMBER       KIND    DATE
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PATENT INFORMATION:     US 6476195         B1   20021105            <--
APPLICATION INFO.:      US 2000-489847          20000124  (9)
RELATED APPLN. INFO.:   Continuation-in-part of Ser. No. WO 1999-US17130, filed
                        on 29 Jul 1999

                               NUMBER        DATE
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PRIORITY INFORMATION:   US 1998-94657P     19980730 (60)
                        US 1998-95486P     19980805 (60)
                        US 1998-96319P     19980812 (60)
                        US 1998-95454P     19980806 (60)
                        US 1998-95455P     19980806 (60)
DOCUMENT TYPE:          Utility
FILE SEGMENT:           GRANTED
PRIMARY EXAMINER:       Jones, W. Gary
ASSISTANT EXAMINER:     Goldberg, Jeanine
LEGAL REPRESENTATIVE:   Human Genome Sciences, Inc.
NUMBER OF CLAIMS:       36
EXEMPLARY CLAIM:        1,7
NUMBER OF DRAWINGS:     3 Drawing Figure(s); 3 Drawing Page(s)
LINE COUNT:             20107
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10537599

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

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'IIIA' IS NOT A VALID FIELD CODE
'IIIA' IS NOT A VALID FIELD CODE
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L15       1668 INHIBIT? (S) GPIIB?

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L3         2407 S ENOS
L4         4256 S L1 OR L2 OR L3
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L6         1678 S L4 AND L5
L7          825 S INHIBIT? (S) SYK
L8          243 S INHIBIT? (S) SYK KINASE
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THIS COMMAND NOT AVAILABLE IN THE CURRENT FILE
Some commands only work in certain files.  For example, the EXPAND
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index.  Enter "HELP COMMANDS" at an arrow prompt (=>) for a list of
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CA INDEXING COPYRIGHT (C) 2009 AMERICAN CHEMICAL SOCIETY (ACS)
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L16 0 PROTEIN TYROSINE KINASE P72SYK

=> file medicine
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FULL ESTIMATED COST	4.59	55.55

FILE 'ADISCTI' ENTERED AT 17:59:35 ON 16 JAN 2009
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CA INDEXING COPYRIGHT (C) 2009 AMERICAN CHEMICAL SOCIETY (ACS)

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L2   2641 S ENDOTHELIAL (S) NITRIC OXIDE SYNTHASE

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L7          825 S INHIBIT? (S) SYK
L8          243 S INHIBIT? (S) SYK KINASE
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L10           9 S L7 AND L6
L11           9 DUP REM L10 (0 DUPLICATES REMOVED)
L12           1 S L11 AND PD<2003
L13        1679 S INHIBIT? (S) CALPAIN
L14           0 S INHIBIT? (S) GPIIB/IIIA
L15        1668 S INHIBIT? (S) GPIIB?

     FILE 'HOME' ENTERED AT 17:43:11 ON 16 JAN 2009

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     MEDLINE, NAPRALERT, NLDB, PHIN, SCISEARCH, TOXCENTER, USPATFULL,
     USPATOLD, USPAT2' ENTERED AT 17:59:35 ON 16 JAN 2009

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L19      39755 L3

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L20      62657 L17 OR L18 OR L19

=> s l5
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=> s l20 and l21

L22       2820 L20 AND L21

=> s l7
L23       4249 L7

=> s l8

L24        933 L8

=> s l23 or l24
L25       4249 L23 OR L24

=> s l25 and l22
L26         11 L25 AND L22

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  14 FILES SEARCHED...
  15 FILES SEARCHED...
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'2003' NOT A VALID FIELD CODE
  19 FILES SEARCHED...
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L28  ANSWER 1 OF 1  USPATFULL on STN
ACCESSION NUMBER:       2002:291062  USPATFULL
TITLE:                  Secreted protein HNFGF20
INVENTOR(S):            Komatsoulis, George, Silver Spring, MD, United States
                        Rosen, Craig A., Laytonsville, MD, United States
                        Ruben, Steven M., Olney, MD, United States
                        Duan, Roxanne D., Bethesda, MD, United States
                        Moore, Paul A., Germantown, MD, United States
                        Shi, Yanggu, Gaithersburg, MD, United States
                        LaFleur, David W., Washington, DC, United States
                        Wei, Ying-Fei, Berkeley, CA, United States
                        Ni, Jian, Rockville, MD, United States
                        Florence, Kimberly A., Rockville, MD, United States
                        Young, Paul, Gaithersburg, MD, United States
                        Brewer, Laurie A., St. Paul, MN, United States
                        Soppet, Daniel R., Centreville, VA, United States
                        Endress, Gregory A., Potomac, MD, United States
                        Ebner, Reinhard, Gaithersburg, MD, United States
                        Olsen, Henrik, Gaithersburg, MD, United States
                        Mucenski, Michael, Cincinnati, OH, United States
PATENT ASSIGNEE(S):     Human Genome Sciences, Inc., Rockville, MD, United
                        States (U.S. corporation)

                             NUMBER       KIND    DATE
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PATENT INFORMATION:     US 6476195         B1   20021105            <--
APPLICATION INFO.:      US 2000-489847          20000124  (9)
RELATED APPLN. INFO.:   Continuation-in-part of Ser. No. WO 1999-US17130, filed
                        on 29 Jul 1999

                               NUMBER        DATE
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PRIORITY INFORMATION:   US 1998-94657P     19980730 (60)
                        US 1998-95486P     19980805 (60)
                        US 1998-96319P     19980812 (60)
                        US 1998-95454P     19980806 (60)
                        US 1998-95455P     19980806 (60)
DOCUMENT TYPE:          Utility
FILE SEGMENT:           GRANTED
PRIMARY EXAMINER:       Jones, W. Gary
ASSISTANT EXAMINER:     Goldberg, Jeanine
LEGAL REPRESENTATIVE:   Human Genome Sciences, Inc.
NUMBER OF CLAIMS:       36
EXEMPLARY CLAIM:        1,7
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NUMBER OF DRAWINGS: 3 Drawing Figure(s); 3 Drawing Page(s)
LINE COUNT: 20107
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, myocardial infarction, myocarditis, ischemia, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis; pulmonary edema and **embolism**, bronchitis and/or cystic fibrosis; Crohn's disease and/or colon cancer. Similarly, the tissue distribution indicates that polynucleotides and polypeptides corresponding to. . .

DETD . . . and rhabdomyosarcoma), as well as cardiovascular and respiratory or pulmonary disorders such as asthma, pulmonary edema, pneumonia, atherosclerosis, restenosis, stoke, **thrombosis** hypertension, inflammation and wound healing. Similarly, polypeptides and antibodies directed to these polypeptides are useful in providing immunological probes for. . .

DETD . . . prevention and/or diagnosis of cardiovasular and respiratory or pulmonary disorders such as asthma, pulmonary edema, pneumonia, atherosclerosis, restenosis, stoke, angina, **thrombosis**, hypertension, inflammation, and wound healing.

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies,. . .

DETD . . . of vascular conditions, which include, but are not limited to, microvascular disease, vascular leak syndrome, aneurysm, stroke, atherosclerosis, arteriosclerosis, or **embolism**. For example, this gene product may represent a soluble factor produced by smooth muscle that regulates the innervation of organs. . .

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies,. . .

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis.

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. The gene product may also be involved in lymphopoiesis, therefore, it can be used. . .

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies,. . .

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise

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DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies,. . .

DETD . . . the cell surface. The aggregation of FcR having immunoreceptor tyrosine-based activation motifs (ITAMs) activates sequentially src family tyrosine kinases and **syk** family tyrosine kinases that connect transduced signals to common activation pathways shared with other receptors. FcR with ITAMs elicit cell. . . ITAM as signal transduction subunits. The coaggregation of antigen receptors or of FcR having ITAMs with FcR having immunoreceptor tyrosine-based **inhibition** motifs (ITIMs) negatively regulates cell activation. FcR therefore appear as the subunits of multichain receptors whose constitution is not predetermined. . .

DETD . . . gene or gene product may also useful in the treatment and/or detection of pulmonary defects such as pulmonary edema and **embolism**, bronchitis and cystic fibrosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies, as tissue. . .

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Polynucleotides and polypeptides of the invention are also useful for the treatment, detection, and/or. . .

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies,. . .

DETD . . . variety of vascular disorders and conditions, which include, but are not limited to miscrovascular disease, vascular leak syndrome, aneurysm, stroke, **embolism**, **thrombosis**, coronary artery disease, arteriosclerosis, and/or atherosclerosis. Furthermore, the protein may also be used to determine biological activity, to raise antibodies,. . .

DETD . . . No. WO 97/34911), Fas Ligand (Takahashi et aL, Int. Immunol., 6:1567-1574 (1994)), VEGI (See, International Publication No. WO 99/23105), a **thrombotic** agent or an anti-angiogenic agent, e.g., angiostatin or endostatin; or, biological response modifiers such as, for example, lymphokines, interleukin-1 ("IL-1"),. . .

DETD . . . limited to, acidic and basic fibroblast growth factors, VEGF-1, VEGF-2 (VEGF-C), VEGF-3 (VEGF-B), epidermal growth factor alpha and beta, platelet-derived **endothelial** cell growth factor, platelet-derived growth factor, tumor necrosis factor alpha, hepatocyte growth factor, insulin like growth factor, colony stimulating factor, macrophage colony stimulating factor, granulocyte/macrophage colony stimulating factor, and **nitric oxide synthase**.

DETD . . . or antagonists of the present invention could also be used to modulate hemostatic (the stopping of bleeding) or thrombolytic activity (**clot** formation). For example, by increasing hemostatic or thrombolytic activity, a polynucleotides or polypeptides, or agonists or antagonists of the present. . .

DETD Myocardial ischemias include coronary disease, such as angina pectoris, coronary aneurysm, coronary arteriosclerosis, coronary

thrombosis, coronary vasospasm, myocardial infarction and myocardial stunning.

DETD . . . Arteritis, aortitis, Leriche's Syndrome, arterial occlusive diseases, arteritis, enarteritis, polyarteritis nodosa, cerebrovascular diseases, disorders, and/or conditions, diabetic angiopathies, diabetic retinopathy, **embolisms**, **thrombosis**, erythromelalgia, hemorrhoids, hepatic veno-occlusive disease, hypertension, hypotension, ischemia, peripheral vascular diseases, phlebitis, pulmonary veno-occlusive disease, Raynaud's disease, CREST syndrome, retinal. . .

DETD . . . include carotid artery diseases, cerebral amyloid angiopathy, cerebral aneurysm, cerebral anoxia, cerebral arteriosclerosis, cerebral arteriovenous malformation, cerebral artery diseases, cerebral **embolism** and **thrombosis**, carotid artery **thrombosis**, sinus **thrombosis**, Wallenberg's syndrome, cerebral hemorrhage, epidural hematoma, subdural hematoma, subaraxhnoid hemorrhage, cerebral infarction, cerebral ischemia (including transient), subclavian steal syndrome, periventricular. . .

DETD **Embolisms** include air **embolisms**, amniotic fluid **embolisms**, cholesterol **embolisms**, blue toe syndrome, fat **embolisms**, pulmonary **embolisms**, and thromoboembolisms. **Thrombosis** include coronary **thrombosis**, hepatic vein **thrombosis**, retinal vein occlusion, carotid artery **thrombosis**, sinus **thrombosis**, Wallenberg's syndrome, and thrombophlebitis.

DETD . . . cell growth, may be employed in treatment for stimulating revascularization of ischemic tissues due to various disease conditions such as **thrombosis**, arteriosclerosis, and other cardiovascular conditions. These polypeptide may also be employed to stimulate angiogenesis and limb regeneration, as discussed above.